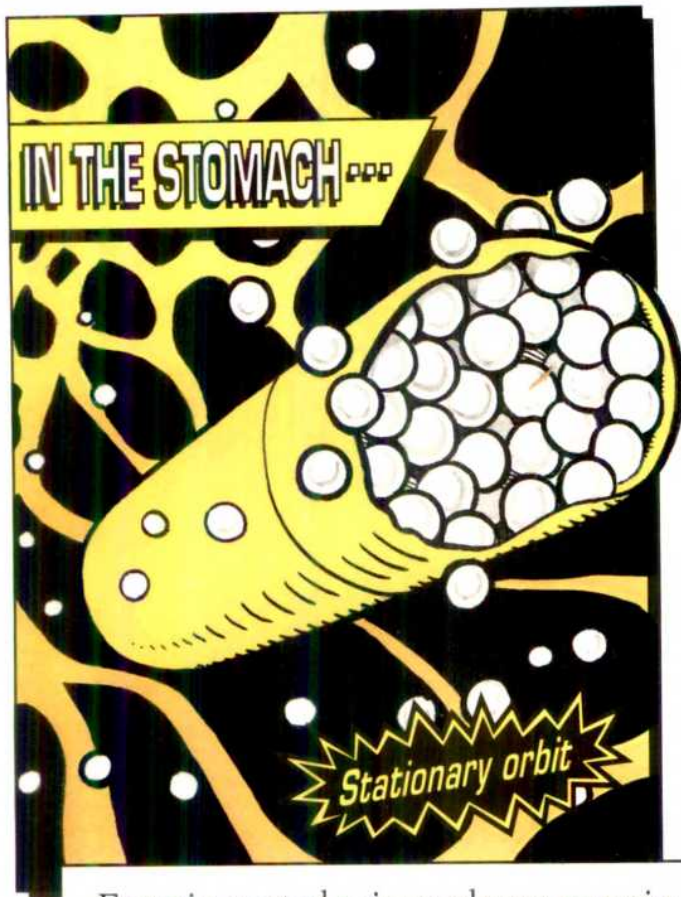
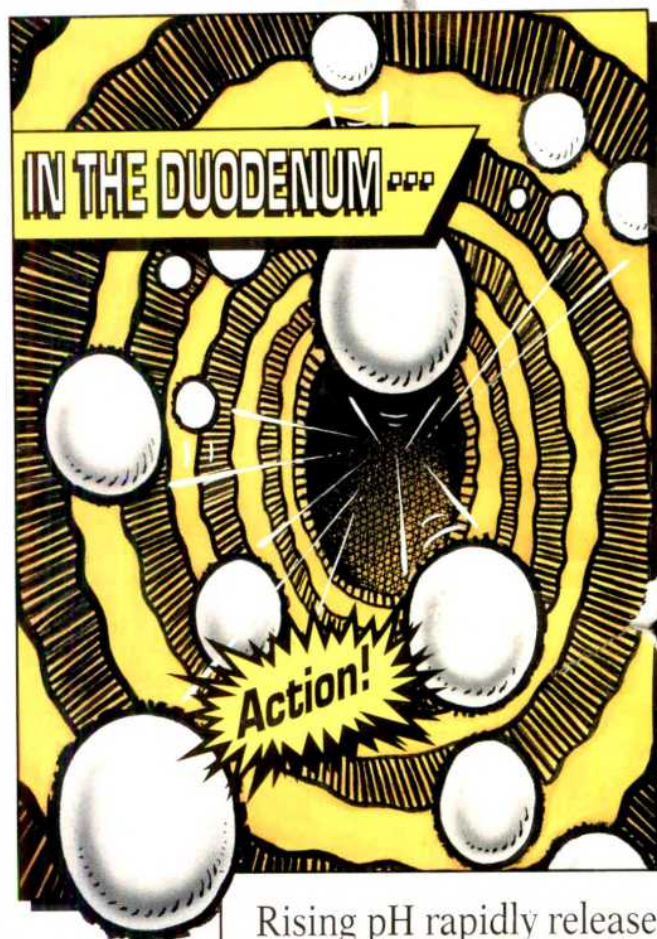


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Contra-indications, Warnings, etc.: Contra-indications: Substitution with pancreatic enzymes is contra-indicated in the early stages of acute pancreatitis.

Warnings: Use in pregnancy: there is inadequate evidence of safety in use during pregnancy.

The product is of porcine origin.

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Product Licence Number: 5727/0001

Name and address of Licence Holder: Kali Chemie Pharma GmbH, Postfach 22

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References

1. Stead RJ et al. *Thorax* 1987;42:533-537. 2. Beverley DW et al. *Arch Dis Child*

1987;62:564-568.

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Cover picture

Società Italiana di Chirurgia

The Italian Surgical Society, founded on 3 April 1882, has its seat in Rome. The first article of the Society's statute declares:

'The Italian Surgical Society is a cultural, non-political institution that encourages the improvement of surgical art and science, facilitates contacts among surgeons, coordinates their work and protects their prestige and legitimate interests.'

To achieve these aims the Society has a Board of Directors

that meets at least monthly. Every year the Board organizes a 4 day Clinical Congress with scientific sessions and post graduate courses. During the Congress the proceedings are distributed.

The Society also publishes *Chirurgia* and the *Bulletin of the Italian Surgical Society*. All these publications and participation in the Congress are free for Fellows. The annual fee is 200 000 Lira (less than £100).

L. Angeli
General Secretary

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Eurosurgery '92

The Editors of the Journal welcome the publication this month of a special supplement of the abstracts presented at the Eurosurgery '92 meeting. This, the Second European Congress of Surgery, is a meeting of national surgical societies with the aim of promoting European collaboration in research and training in surgery. After its first successful meeting in Paris, in 1990, the Editors wish the organizers of Eurochirurgie/Eurosurgery every success with the second meeting in Brussels.

The Journal supports this collaborative venture among European surgeons. The quality and diversity of the abstracts published in the supplement to this issue are adequate testimony to the wide-ranging activities of European surgeons in clinical and experimental spheres.

We hope to publish a selection of papers based on presentations at this meeting, and any author who has not yet submitted a manuscript is invited to do so. Manuscripts already submitted will be considered expeditiously, and the Editors hope to publish a special Eurosurgery issue early in 1993.

We wish all those attending the Eurosurgery meeting good surgery, good science and good fellowship.

**R. C. N. Williamson
J. R. Farndon
J. A. Murie
C. D. Johnson**

The Editors of The British Journal of Surgery

Br. J. Surg. 1992, Vol. 79, June,
482-483

Continuing our series, which started last month with the Chairman and Vice-Chairmen of The British Journal of Surgery Society, we now present the Editorial Team of the Journal.

Senior Editor

PROFESSOR ROBIN WILLIAMSON



Robin Charles Noel Williamson (born 1942) graduated from Emmanuel College, Cambridge and St Bartholomew's Hospital, London. As student editor of the Bart's journal in 1964 he obtained a foretaste of the fun to be had from wielding the editorial blue pen (an experience that he managed to avoid repeating for another 24 years). Following junior clinical attachments in London and the home counties he moved steadily westwards, first to Reading (as registrar), next to Bristol (as senior registrar) and then to the Massachusetts General Hospital, Boston (as Clinical and Research Fellow). Returning to Bristol in 1977, he soon found himself stranded in an academic department without a Head and after an uneasy interregnum was eventually appointed to the Chair of Surgery at that University in 1979. In 1987 he survived a mid-career transfer to become Professor and Director of Surgery at the Hammersmith Hospital and the Royal Postgraduate Medical School. The move to the Hammersmith has allowed him to concentrate on his first love, namely pancreatic surgery. He is current Secretary-General of the World Association of Hepato-pancreatobiliary Surgery, which permits him to indulge another love, namely international travel and camaraderie. He became Secretary of The British Journal of Surgery Society in 1983 and seemed wedded to the managerial side of the Journal until his sudden switch to the editorial side last year. As Senior Editor he is responsible for receiving original articles, choosing the referees, digesting their opinions and reaching at least an interim verdict on the fate of all manuscripts submitted. Perhaps the necessary thick skin was acquired in the editorial chair at Bart's.

Editor

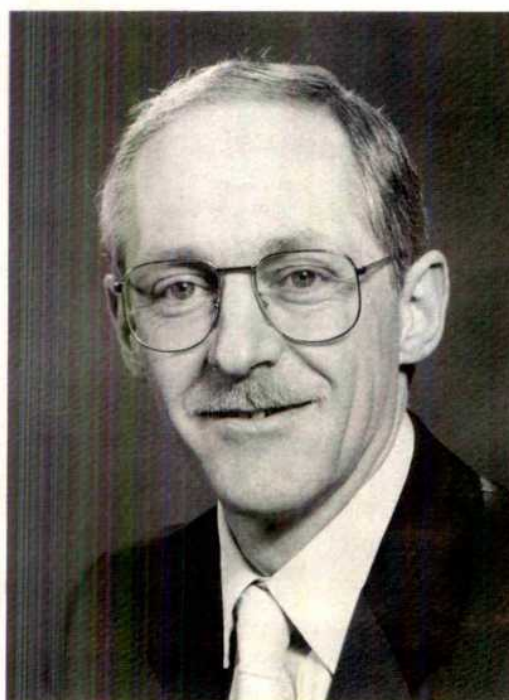
PROFESSOR JOHN FARNDON



John Richard Farndon was born in 1946 and has been Professor of Surgery in the University of Bristol since 1988, succeeding to the Chair when Robin Williamson moved to London. It is a curious coincidence that the first Editor of *The British Journal of Surgery* in 1913, Ernest William Hey-Groves, was also a Clinical Professor of Surgery at Bristol. Before moving to Bristol, John Farndon had been a Newcastle man through and through, gravitating from medical student to Consultant Senior Lecturer on the banks of the River Tyne. He has remained equally faithful to endocrine surgery, with BSc in Anatomy (first class honours) on the embryology of the parathyroid gland and an MD on pheochromocytoma. Besides endocrine surgery, active clinical interests are breast disease and pancreatic transplantation. Distinctions awarded include scholarship from the Peel Trust and the James IV Association of Surgeons, a Hunterian Professorship and the Pybus Lecture and Medal. He is current Secretary of the Surgical Research Society. Professor Farndon became Associate Editor of the Journal in 1989 and Editor in 1991. He joined the Council of The British Journal of Surgery Society in 1991. As Editor, John Farndon helps with the regular handling of articles submitted to the Journal and plays a major role in improving many of the manuscripts accepted for publication. He has also taken responsibility for the reciprocal digests of each other's journals that we have recently introduced with *The American Journal of Surgery* and *Der Chirurg*.

Review Editor**MR JOHN MURIE**

John Andrew Murie was born in 1949 and qualified with honours at Glasgow University in 1975, having already obtained first class honours in his BSc degree. He won a string of undergraduate prizes and obtained distinctions in seven subjects. En passant he obtained a Carnegie Scholarship to visit Minneapolis in 1974. His surgical training was in Glasgow, likewise his FRCS, but he moved to Oxford as an academic consultant surgeon (Clinical Reader) in 1984 and from there to Edinburgh in 1989. While at Oxford, John Murie was heavily involved in renal transplantation, but his higher degree (MD Glasgow) was in the field of carotid artery disease, and his major clinical interest remains vascular surgery. He has retained a close association with the Royal College of Physicians and Surgeons of Glasgow, winning the Alexander Fletcher Memorial Prize (1985) and the May and Baker Essay Prize (1986) and serving as an FRCS examiner (1987 onwards). Mr Murie became Associate Editor of the Journal in 1989 (at the same time as Professor Farndon) and a Member of Council of the BJS Society 2 years later. In 1991 he was appointed Review Editor with particular responsibility for leading articles, review articles and book reviews.

Associate Editor**MR COLIN JOHNSON**

Colin David Johnson (born 1952) is the youngest member of the Editorial Team. He was an undergraduate at King's College, Cambridge, where he obtained the Barcroft Prize in Physiology plus a BA degree in Medical Sciences and Anglo-Saxon (providing useful vocabulary for an Editor). He then studied clinical medicine at the London Hospital, qualifying in 1976. Mr Johnson was awarded a Travelling Fellowship by the Medical Research Council to work in Marseille (1980–1982), where he studied pancreatic physiology – to gain a Cambridge MChir – and French to supplement his Anglo-Saxon. Service as registrar in Bristol included an attachment to the Senior Editor's firm but was soon relieved by a senior registrar post at the Westminster Hospital. Colin Johnson has been Consultant Senior Lecturer at Southampton since 1988. His clinical and academic interests are centred on HPB surgery in general and pancreatic surgery in particular. In 1990 The British Journal of Surgery Society awarded him a European Travelling Fellowship and the following year he joined the Editorial Team; his credentials as Supplement Editor for the 1992 EuroSurgery meeting are thus impeccable. As Associate Editor Mr Johnson devotes most of his time to sub-editing accepted papers.

Robin Williamson

Primary aldosteronism

The signs and symptoms of primary aldosteronism are non-specific and common. The disease is characterized by hypertension and hypokalaemia, caused by excessive aldosterone secretion. Differential diagnosis between the various subgroups of primary aldosteronism remains a problem in endocrinology. The first reported patient with hyperaldosteronism had an adrenocortical adenoma and was cured after unilateral adrenalectomy¹. Initially, it was believed that 10–20 per cent of hypertensive patients might have primary aldosteronism which could be improved by operation², but more recent studies³ have estimated the prevalence of primary aldosteronism among hypertensives at between 0.05 and 2 per cent. Such a rare disease is easily overlooked. A mean duration of hypertension of 7–8 years before diagnosis of primary aldosteronism demonstrates the importance of clinical awareness⁴. Furthermore, several subtypes of primary aldosteronism have been recognized which need to be distinguished from each other and which require different treatments⁵.

Classification of the different forms of primary aldosteronism is based on endocrinological and radiological evaluation. Patients must be potassium repleted, have an adequate sodium intake, and antihypertensive drugs should be withheld to remove their influence on the renin–angiotensin–aldosterone system. For a patient with suspected hyperaldosteronism, investigation is best started by determining 24-h urinary aldosterone excretion and plasma renin activity. High urinary aldosterone excretion and low plasma renin activity are consistent with primary aldosteronism. At this stage a more sophisticated endocrinological investigation should be initiated.

The six subgroups of primary aldosteronism so far recognized are: (1) adrenocortical adenoma; (2) bilateral adrenocortical hyperplasia (idiopathic hyperaldosteronism (IHA)); (3) adrenocortical carcinoma; (4) glucocorticoid-suppressible hyperaldosteronism; (5) renin-responsive adrenocortical adenoma; and (6) primary adrenocortical hyperplasia. More than 60 per cent of patients with primary aldosteronism have a single benign adrenocortical adenoma; about 20 per cent have IHA^{5,6}.

The adenomas are usually adrenocorticotrophic hormone (ACTH) dependent while IHA is renin–angiotensin dependent⁷. Thus, patients with adenomas have a cortisol-like plasma aldosterone diurnal variation. The ACTH-dependent disease can also be demonstrated by a postural test showing decreased or constant levels of plasma aldosterone when changing from rest to ambulation. A postural increase of plasma aldosterone favours a renin–angiotensin-dependent disease⁷. An aldosterone-producing adrenocortical carcinoma responds to neither ACTH nor angiotensin⁷; it is usually >5 cm in diameter and has a pathological steroid production⁸. Glucocorticoid-suppressible hyperaldosteronism is identified by a dexamethasone suppression test and the two last subgroups are extremely rare.

Localization should not be undertaken until the diagnosis is established, as non-hyperfunctioning adrenal tumours are common in the hypertensive population. A majority (80 per cent) of aldosterone-producing adrenocortical tumours are >1 cm in diameter and are detectable by computed tomography, magnetic resonance imaging and ultrasonography³. However, small (<1 cm in size) intraglandular aldosterone-producing adenomas do exist, and so in many cases of primary aldosteronism it is advisable to perform localization not only of a tumour, but also of hyperfunction. A high aldosterone:cortisol ratio in the adrenal venous effluent provides the best localizing accuracy, with a precision of up to 95 per cent³. Adrenal scintigraphy using 6 β -[¹³¹I]iodomethyl-19-norcholesterol during dexamethasone inhibition of the adrenal cortex provides a functional localization of just over 70 per cent in primary aldosteronism⁹.

For patients with a unilateral adrenocortical adenoma, a unilateral ACTH-dependent hyperplasia, or an adrenocortical carcinoma, adrenalectomy should be performed. We prefer an extraperitoneal approach using a flank incision. Resecting the 11th or 12th rib offers excellent exposure for smaller benign lesions, and a thoracoabdominal incision is reserved for large and often malignant tumours. Patients with IHA and glucocorticoid-suppressible hyperaldosteronism should be managed medically, with spironolactone and glucocorticoids respectively.

The typical aldosterone-producing adrenocortical adenoma has a golden-yellow colour and may be completely or partially encapsulated. Large, lipid-laden, clear zona fasciculata-like cells dominate, and the adjacent cortex is slightly atrophic⁶. In atypical cases adenomas, nodules and hyperplasia may coexist and a definite histopathological diagnosis cannot always be obtained.

Most patients with an aldosterone-producing adrenal adenoma become normotensive within a few days of operation and long-term cure rates vary from 69 to 89 per cent^{3,4,10}. Those with persistent hypertension respond favourably to conventional antihypertensive treatment. The results of adrenal surgery for primary aldosteronism depend mainly on the accuracy of preoperative biochemical evaluation and tumour location.

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Laparoscopy and assessment of digestive tract cancer

Laparoscopy has been widely used for many years by gynaecologists and some gastroenterologists as a diagnostic and therapeutic tool. Yet, except by a few enthusiasts, it has been little used in general surgery. Now, however, with the explosive development of minimally invasive surgery, it seems that laparoscopic techniques will play an increasingly important role in the diagnosis and treatment of cancer of the digestive tract¹.

Despite the introduction of ultrasonography, computed tomography (CT), and magnetic resonance imaging, the surgeon dealing with gastrointestinal malignancy is often faced with a wide discrepancy between preoperative and intraoperative staging. There are certain tumours, for example of the stomach and colon, for which the surgeon may be committed to resection at operation even if only palliation may be achieved². In such instances staging and decision making can take place during laparotomy. However, for patients with cancer of the oesophagus, gastric cardia, pancreas, or liver, surgery is neither the only nor always the best palliative treatment; in such cases more accurate staging before operation should prevent unnecessary laparotomy.

Laparoscopy can provide valuable information that should lead to a more accurate staging of gastrointestinal malignancies. It permits inspection and indirect 'palpation' of the primary tumour site and the general abdominal cavity (including the lesser sac) to assess both local and peritoneal spread. Furthermore, it allows retrieval of cytological and histological specimens for diagnostic confirmation of the primary tumour, lymph node spread, and hepatic or peritoneal metastases.

Watt *et al.*³ demonstrated the value of laparoscopy by comparing it with ultrasonography and CT for detection of intra-abdominal metastases in cancer of the oesophagus and gastric cardia. They showed prospectively that laparoscopy was significantly more sensitive and accurate than either ultrasonography or CT with respect to hepatic status. Laparoscopy also performed best with respect to nodal metastases, although this was statistically significant only when compared with the sensitivity of ultrasonography. Neither ultrasonography nor CT detected any peritoneal metastases, while laparoscopy detected eight of nine cases. The authors concluded that laparoscopy is a safe and reliable method of determining intra-abdominal tumour status and may obviate the need for surgery in some patients with malignant dysphagia.

It is probable that laparoscopy will allow significant advance also in the area of hepatic and pancreatic surgery. Cuschieri⁴ and colleagues have repeatedly shown that laparoscopy is a useful procedure for diagnosing and staging in patients with pancreatic cancer, by obtaining target biopsies and cytology of the primary tumour or secondary intraperitoneal deposits. Warshaw *et al.*⁵ have also demonstrated that, although CT gives useful information about the size of a tumour, it does not successfully detect peritoneal metastases; laparoscopy on the other hand detects peritoneal metastases with 96 per cent sensitivity and provides important information about the resectability of pancreatic cancer. The value of laparoscopy has also been shown in the diagnosis and staging of primary carcinoma of the gallbladder⁶.

The limitations of laparoscopy lie in the evaluation of less obvious hepatic and retroperitoneal malignancies, and it is here that intraoperative ultrasonography, performed during laparotomy, has proven its value. Rifkin *et al.*⁷ obtained additional information leading to a change in surgical approach in no fewer than 31 per cent of patients with liver tumours. We have found similar results using this technique in screening for liver metastases from colorectal cancer⁸. Determining the exact diagnosis of hepatic lesions, their number and precise localization, is imperative when considering liver resection or adjuvant therapy; conventional ultrasonography, CT and magnetic resonance imaging all appear to be inferior to intraoperative ultrasonography.

It is now technically possible to perform ultrasonography via the laparoscope, enabling exploration of both liver parenchyma and the retroperitoneum using high resolution ultrasonographic probes⁹. The advantages of combined laparoscopy and ultrasonography are numerous and we believe the technique might even replace other

preoperative radiological investigations. Further refinements of trocars and transducers may allow laparoscopy with ultrasonography to be performed under local anaesthesia on an outpatient basis.

In summary, diagnostic laparoscopy, performed immediately before a planned laparotomy, is a safe and reliable technique that provides valuable information needed for the accurate assessment and appropriate management of gastrointestinal malignancies. It is likely to play an increasing role in this context in the future and, with the addition of intraoperative ultrasonography, should prove to be a significant advance.

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Screening for large bowel neoplasms in individuals with a family history of colorectal cancer

Logistical problems associated with population screening for colorectal cancer are identified and the possibility of targeting screening to those with a familial predisposition to the disease is discussed. Evidence for a substantial genetic effect on the overall incidence of colorectal cancer is reviewed. The screening detection rate of colorectal neoplasms in relatives of patients with colorectal cancer has been shown to be higher than that expected in a non-selected population; the evidence that polypectomy will reduce future colorectal cancer risk in such individuals is explored. Recent advances in the molecular genetics of colorectal cancer susceptibility are reviewed; it is possible that a genetic test might be developed in the future which could identify at least a proportion of those at risk. Excluding financial considerations, the risk-benefit ratio of colonoscopy in a screened population is intimately related to the remaining risk of colorectal cancer in those who undergo the examination. At present, patients undergoing colonoscopy to investigate a positive faecal occult blood (FOB) test as part of a population-based screening programme include individuals with a familial predisposition as well as those without. About 20 per cent of all cases of colorectal cancer are associated with an obvious genetic predisposition, and the risk of cancer in their relatives is high. Because false positives occur with Haemoccult, the residual risk to the population who are FOB positive but do not have a familial trait may be sufficiently low that the dangers of colonoscopy could outweigh the potential benefits. Scotland has a high incidence of colorectal cancer, and analysis of recent Scottish incidence data shows an actuarial lifetime risk of developing this disease of one in 23 for men and one in 33 for women. As a family history of the disease increases that risk by two to four times and the neoplasms arise throughout the colon in such a group, there may be a case for offering colonoscopy to all first-degree relatives of those under 50 years of age at diagnosis, if not of all index cases of colorectal cancer.

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Colorectal cancer is second only to lung cancer as a cause of death from malignancy, accounting for approximately 20 000 deaths annually in the UK and over 70 000 a year in the USA. Although the 5-year survival rate for colorectal cancer has improved in the UK, the incidence of the disease has increased concomitantly and so the mortality rate from the disease has scarcely changed in 50 years. Despite a wealth of knowledge on the natural history of the neoplastic change in the colorectum¹, more than 90 per cent of tumours are detected when transmural spread has already occurred and surgery is unlikely to result in cure^{2,3}. Hence, there has been a move to screen asymptomatic individuals in an attempt to detect early neoplasms, which may be more amenable to treatment. The screening approach is intuitively appealing but, although there is substantial indirect evidence suggesting survival benefit, there is no conclusive proof. Owing to a deficit of cardiovascular mortality in patients with colorectal cancer⁴ and their relatives⁵, prevention of death by large bowel screening may also result in a further, as yet unseen, reduction in the all-cause mortality rate. However, until completion of the current randomized controlled trials of faecal occult blood (FOB) screening, population screening for colorectal cancer cannot be

recommended in the UK. Nevertheless, the then Federal Republic of Germany introduced nationwide screening for those over 45 years of age by digital rectal examination in 1971 and by FOB testing in 1977. In the USA, colorectal cancer screening is now formally recommended⁶ and comprises an integral part of the multisystem check-up offered in many private clinics. Some authors are vehemently against any form of cancer screening⁷ and others have questioned the value of polypectomy as a means of reducing the chance of future colorectal malignancy⁸. In addition, it has been calculated from available data that, because of the occurrence of false-positive FOB tests, the risks of population-based screening could outweigh the benefits⁹. There is certainly a need for some circumspection to allow time for properly controlled evaluation of the ethical, financial, social and medical effects before the wholesale introduction of yet more cancer screening programmes¹⁰.

Population screening for colorectal cancer has been well reviewed elsewhere^{6,11}. This paper explores the case for screening individuals who have a family history of the disease and discusses the methods available. Patients with colorectal cancer who have a family history of this disease are younger than those with no such familial tendency^{12,13}. Hence,

evaluation of screening in such high-risk groups must take into account economic implications that are not applicable to population-based screening programmes. Individuals with a genetic susceptibility to colorectal neoplasia can be identified on the basis of empirically derived risk estimations. It is also possible that molecular genetics may eventually be able to identify at least a proportion of individuals who carry genetic lesions predisposing to colorectal neoplasia.

Logistical problems of population screening for colorectal cancer

Five controlled studies designed to assess the effect of population-based FOB screening on colorectal cancer mortality rates are currently under way¹⁴⁻¹⁸. Although several of the trials show that the cancers detected are at a more favourable stage (50-70 per cent Dukes' A) than those detected in the non-screened groups (5-10 per cent Dukes' A), the data are not sufficiently mature to determine whether there is a resultant survival benefit. However, if it is assumed that benefit can be demonstrated, the burden to health service resources will be substantial in terms of follow-up examinations, such as colonoscopy. The extra workload can be estimated by extrapolating the data from the Nottingham study to the UK as a whole¹⁸. The screening age band is 50-75 years and there is a reasonably stable population of 14 million people in the UK within this age range. Even with well motivated general practitioners and within the confines of a well conducted trial, compliance is only 55 per cent, leaving 7.7 million who might take up the offer of screening. Using a biannual screening protocol would mean an annual workload of 3.85 million individuals undergoing FOB tests, with three samples for each of these persons screened. There are approximately 27 000 registrations of colorectal cancer in the UK each year and the overall sensitivity for Haemocult (Roehm, Derby, UK) testing has been calculated indirectly by Hardcastle *et al.*¹⁸ as 55 per cent, while 16 per cent of cancers occur in individuals under 50 or over 80 years of age where screening will have no effect. This, combined with compliance data, means that a nationwide FOB screening programme can hope to detect a maximum of only 6861 cancers annually (25 per cent of the UK annual incidence). Further investigation of positive FOB tests will result in a substantial increase in colonoscopy; again the projected workload can be estimated from the Nottingham data. When taking into account those being screened for the first time, those being rescreened, those leaving the screening age band having been negative on at least one occasion, and those entering the screening programme at age 50 years, the frequency of positive 2-yearly FOB tests with dietary restriction could be expected to be about 2.0 per cent. Therefore, an extra 77 000 colonoscopies will be required each year in the UK. Clearly, if the survival benefit is substantial, such consumption of resources will be worthwhile. Using a complex mathematical model and certain fundamental (and unproven) assumptions, it has been calculated that an annual FOB test would prevent 71 per 10 000 men screened dying from the colorectal cancer that they would have developed had they not been screened, with a similar but slightly lower benefit for women⁶. However, this translates to a mean increase in life expectancy of only 30.6 days for the screened population as a whole.

A further practical problem of follow-up investigation after a positive FOB test is that all invasive procedures carry a finite risk of colonic perforation and of resultant mortality^{19,20}. Hence, the chance that the patient will benefit from the screening procedure must substantially outweigh the risk of harm from it. The predictive value of a positive FOB test is about 10 per cent for cancer and 50 per cent for adenomas > 1 cm in size and/or cancer¹⁸. It is not known whether the detection and removal of smaller adenomas is worthwhile, but it must be considered that the FOB test may not detect these lesions in a discriminatory manner²¹. Random colonoscopy in a comparable population reveals a similar prevalence of smaller

adenomas²². At present the balance of benefit does seem to lie in favour of further investigation of a positive FOB test, although it has been suggested that an acceptable risk-benefit ratio for FOB testing can be achieved only in those over 70 years of age⁹. The quality of the administration and analysis of the FOB tests is crucial, as any increase in sensitivity for detecting cancer and larger adenomas must be balanced against lower specificity and the resultant increase in morbidity and mortality rates from second-line investigation of a positive test.

The logistical and practical problems of population screening for colorectal cancer by FOB testing should not be underestimated. The results of the current trials must be awaited before the question of whether there is a survival benefit can be formally addressed, and before calculations can be made on the sensitivity and overall accuracy of the test (due to a lack of true controls)⁹.

Targeted screening for colorectal cancer

One approach to early detection of colorectal cancer is to identify those most likely to develop the disease and then to target such groups for intensive screening. Such targeted screening may be a more efficient, and cost-effective, method of detecting early neoplasms than population screening and should have a more favourable risk-benefit ratio. One factor that indicates an increase in colorectal cancer risk is a positive family history of the disease. The increased risk is sufficiently high in some individuals to warrant invasive screening procedures such as colonoscopy, with the added option of therapeutic intervention at the same procedure.

There is substantial evidence suggesting a strong genetic component in the overall incidence of colorectal cancer. A significantly greater proportion of patients with colorectal cancer has a family history of the disease than of a control population, with various studies reporting a family history in 11-20 per cent of new cases^{13,23-27}. The overall relative risk of colorectal cancer for first-degree relatives of patients is variously calculated at between two and four^{23,27-31}. There is also a threefold increased risk of adenomas developing in relatives of patients with colorectal adenoma or carcinoma^{30,32}. Using a computer model, Eddy *et al.* have calculated a lifetime risk of developing colorectal cancer for all relatives of a patient with cancer of 11 per cent¹⁹. Using Lovett's data²⁵, calculations have been made which stratify the risk of dying from colorectal cancer according to the extent of family history (Table 1)³³. Such *ad hoc* risk calculation avoids the problem that several family members have to be afflicted with cancer before it is realized that surviving family members have a high risk of colorectal malignancy.

It is important to note that the raw data used by Houlston *et al.*³³ in the calculation of lifetime risk were for the period 1969-1973 and, owing to the specialist nature of St Mark's

Table 1 Lifetime risk of colorectal cancer in London and Scotland

	1971	1989
Population risk	1 in 50*	—
One relative affected	1 in 17*	—
One first- and one second-degree relative affected	1 in 12*	—
One relative of under 45 years affected	1 in 10*	—
Two first-degree relatives affected	1 in 6*	—
Dominant family history	1 in 2*	—
Scottish incidence risk†		
Men	1 in 31	1 in 23
Women	1 in 37	1 in 33
Scottish mortality risk†		
Men	1 in 38	1 in 50
Women	1 in 46	1 in 65

*Colorectal cancer mortality data 1969-1973, London, from Houlston *et al.*³³ (1971 taken as the midpoint of the study); †Information and Statistics Division, Scottish Health Service Common Services Agency

Hospital, were derived from a highly selected patient population with an excess of rectal cancer. Scotland has a high incidence of colorectal cancer and Table 1 shows the actuarial Scottish colorectal cancer incidence and mortality data from 1971 (the midpoint of the Lovett study²⁵) and 1989 (R. Black, personal communication, Information and Statistics Division, Scottish Health Service Common Services Agency). The risk of dying from colorectal cancer when all-cause mortality is taken into account was substantially greater in Scotland than in London in 1971. However, the risk of death from colorectal cancer has reduced quite markedly from 1971 to 1989, whereas the chance of developing the disease has increased by 31 per cent for men and 12 per cent for women over this period. Therefore, assuming an increased relative risk of three due to a positive family history, a Scottish man with such a family history currently has a one in 7.5 chance of developing and a one in 17 chance of dying from colorectal cancer; the respective numbers for a woman are one in 11 and one in 22. These figures accord well with the 11 per cent lifetime risk of colorectal cancer calculated for the USA population with an affected relative¹⁹. It can be appreciated that having even one relative with colorectal cancer increases the chance of developing malignancy to a level at which intensive screening is indicated.

There is conflicting evidence as to whether the influence of age at diagnosis on the risk of cancer in relatives of the index case reported in the Lovett study is due to a genetic effect. Cancer family syndrome makes up 29–39 per cent of those under 50 years at diagnosis¹² and the rate of a positive family history in those under 50 years was twice that of those over 50 years of age in another study¹³. However, other work has failed to demonstrate an effect of age^{27,30}. These apparent discrepancies may be due simply to the confounding effect of older index cases having larger and older families.

Included within the group of individuals with a positive family history are kindreds with hereditary non-polyposis colorectal cancer (HNPCC). It has been shown that about 5 per cent of all cases of colorectal cancer occur in members of HNPCC kindreds^{12,34} and a sevenfold increased risk of death from colorectal cancer has been calculated for members of such families³⁵, corresponding to an overall lifetime risk of one in six. Hence, cancer screening in such kindreds is considered obligatory by some authors³⁶.

The observed familial clustering of colorectal cancer cases appears to be due to shared genes, which influence a carrier's response to environmental factors, rather than simply to shared exposure to environmental carcinogens, because the incidence in spouses of affected individuals is the same as that of the population as a whole^{32,37}. It is possible that this observation could be explained on the basis of premarital exposure to an aetiological dietary factor in the parental home, but this seems highly unlikely given the age distribution of the disease. In any case, in terms of a large-scale screening programme, the mechanism of the observed increased risk (whether genetic or shared environment) is immaterial because the increased relative risk is derived empirically from clinical observation.

The bulk of available epidemiological evidence strongly implicates genetic susceptibility as the major contributor to the increased risk affecting first-degree relatives of patients with colorectal cancer. Similarly, data from a prospective endoscopic screening study³² of 640 relatives of 34 index cases with colorectal neoplasia best fitted a model for a single gene defect predisposing to colorectal adenomas and carcinomas, with 19 per cent of the general population carrying the susceptibility gene. Most striking of all, the study suggested that cases occurred only where there was a genetic susceptibility. It appears that the observed susceptibility to colorectal cancer in relatives of patients with the disease is due to the inheritance of susceptibility to adenoma. It also seems likely that more than one susceptibility gene could be involved in separate families. Further somatic genetic events brought about by environmental factors might then confer selective growth advantage on certain clones in a 'primed' epithelium, leading eventually to the full malignant phenotype³⁸.

Prevalence of colorectal neoplasms in relatives of patients with colorectal cancer

It seems likely that the observed increased incidence and mortality rate from colorectal cancer in relatives of patients with this disease is due to a higher prevalence of adenomas rather than to a more aggressive adenoma–carcinoma sequence in such individuals. However, it is possible that both influence colorectal cancer risk. Several screening studies have shown an increased prevalence of colorectal neoplasms in relatives with adenomas and carcinomas. Woolf reported one of the earliest studies of the prevalence of adenomas in close relatives of patients with colorectal cancer²³. Rigid sigmoidoscopy revealed adenomas in 45 per cent of relatives and only 5 per cent of spouses. Subsequently, many endoscopic screening studies have shown that the prevalence of colorectal neoplasms in individuals with a family history of colorectal cancer is higher than that in an unselected screened population. The detection rate has been variously reported as 8.1³⁹, 9.4⁴⁰, 12.4^{41,42}, 12.5⁴³, 13.4⁴⁴, 17.4⁴⁵, 17.5³³, 18.4⁴⁶, 19.3³², 21.4⁴⁷, 25.4⁴⁸, 27.4⁴⁹, 28.5⁵⁰ and 63.3⁵¹ per cent. Three prospective controlled studies^{32,39,42} demonstrated an increased detection rate of benign and malignant colorectal tumours in the presence of a positive family history, and in two studies this was statistically significant^{32,39}. The prevalence of carcinomas and adenomas >1 cm in size in other, non-selective, endoscopic screening studies has been reported as 5.5⁵², 5.5⁵³, 3.4⁵⁴ and 5.8⁵² per cent. Although autopsy series show that about one-third of colons carry neoplasms^{55–57}, it is not wholly valid to compare data from endoscopic studies with autopsy findings, because colonoscopy will certainly underestimate the true adenoma prevalence, especially those <1 cm in size. In addition, the mean age of the screened individuals was lower in the endoscopic series referred to above than in the autopsy series and adenoma prevalence at autopsy has been shown to increase with age⁵⁷. It is also notable that there are no autopsy studies comparing the prevalence of neoplasms in those with and those without a family history.

Further evidence suggesting that the increased colorectal cancer risk in relatives of affected individuals is due to a familial predisposition to the formation of adenomas rather than to a predisposition to a more aggressive adenoma–carcinoma sequence comes from analysis of Lovett's data²⁵ by Morson *et al.*¹. They assessed the numbers of synchronous adenomas present in the resection specimen from the index cases with cancer and correlated this with the degree of family history. The mean number of adenomas was 1.2 in patients from one-case families, 2.2 for two-case families and 4.3 for three-case families. Although this analysis may be influenced by the small numbers involved, particularly of three-case families, it is supported by the increased prevalence of adenomas in relatives of patients with adenoma or cancer in other studies^{30,32,39}. Although those with a family history of colorectal cancer may simply develop more adenomas, there is some evidence that the adenoma–carcinoma progression may be more or less aggressive depending on family history. Degree of dysplasia in the adenomas detected by Morson *et al.* was correlated with the extent of the family history¹. In addition, in molecular genetic studies, the proportion of chromosomal locations exhibiting loss of genetic material (fractional allele loss) in colorectal cancer tissue has also been shown to correlate with family history of the disease⁵⁸.

Optimal method of detecting colorectal neoplasia in those with a family history

Family history may serve as an enrichment criterion indicating a need for second-line screening measures in much the same way as FOB testing is used in population screening programmes. The optimum method of screening is necessarily influenced by economic as well as medical considerations. FOB testing is relatively cheap and simple, but lacks the sensitivity of endoscopic examination of the colon. A projected 33 per cent

Table 2 Identification of individuals carrying colorectal neoplasms by flexible sigmoidoscopy alone or by colonoscopy

Reference	Screened population	Individuals with adenomas	
		Flexible sigmoidoscopy alone	Colonoscopy
Guillem <i>et al.</i> ⁴⁸	48	8	12
Grossman and Milos ⁴⁶	154	16	28
Baker <i>et al.</i> ⁴⁹	201	29	54
Herrera <i>et al.</i> ^{44*}	200	19†	38†
McConnell <i>et al.</i> ⁴¹	125	9	15
Orrom <i>et al.</i> ⁴⁷	114	24	29
Foutch <i>et al.</i> ^{62*}	114	17	47
Total	956	122	223

*Sequential flexible sigmoidoscopy and colonoscopy study; †inferred data on 200 individuals from the 70 who were negative on flexible sigmoidoscopy and went on to undergo colonoscopy, seven of whom had neoplasms not detected by the initial distal examination

reduction in colorectal cancer mortality rate has been calculated for asymptomatic individuals with a family history of the disease by employing annual FOB screening, whereas the reduction would be 85 per cent for colonoscopic screening¹⁹. However, screening studies have suggested that testing for FOB by Haemocult is not sufficiently sensitive in high-risk individuals^{33,39,50,59}, having a negative predictive value of only 78 per cent³³. Newer immunological tests for FOB, which are highly sensitive but lack the specificity required for population screening, may be valuable in screening such groups.

A high proportion of colorectal cancers arising in those with familial predisposition occurs in the right colon, out of reach of the flexible sigmoidoscope^{47,60,61}. It has been suggested that flexible sigmoidoscopy is the most appropriate and cost-effective screening procedure²⁷. However, having identified a group at such high risk, it seems inappropriate to carry out an incomplete examination and perhaps give false reassurance to individuals with proximal colonic tumours. In one study of 200 patients with a family history of colorectal neoplasia, screening by flexible sigmoidoscopy identified 19 individuals (10 per cent) with neoplasms⁴⁴. Seventy patients who were negative on distal colonic examination then accepted an invitation for colonoscopy and a further seven (10 per cent) were found to have neoplasms. Therefore, flexible sigmoidoscopy had a sensitivity of only 50 per cent and a negative predictive value of 90 per cent. This is supported by another study of sequential flexible sigmoidoscopy followed by colonoscopy in men over 50 years of age not selected on the basis of family history⁶². Flexible sigmoidoscopy had only a 63 per cent sensitivity and an 80 per cent negative predictive value. Combining the raw data from all prevalence screening studies in which lesions were biopsied and which assessed the detection rate of flexible sigmoidoscopy compared with colonoscopy^{41,44,46-49,62}, it can be calculated that flexible sigmoidoscopy has a sensitivity for detecting colorectal neoplasms of only 55 per cent and a negative predictive value of 88 per cent (Table 2).

Value of early detection and removal of colorectal neoplasia

It is not known whether there is a major influence of lead time (early diagnosis of cancer but natural history unaffected) or length time (less aggressive cancers detected by screening because the tumour is present for longer) biases in the early detection of colorectal cancer in screening studies. Because of such potential biases, classic retrospective studies correlating long-term survival (equating to cure) with early pathological tumour stage^{63,64} tend to be discounted, and so the prospective-controlled trials of mass population screening by FOB testing must be awaited to determine whether the observed increase

in the detection of early cancers by screening does indeed translate into a reduction in mortality rate.

Since not all adenomas become carcinomas¹ and there have been no properly controlled trials of polypectomy, the value of removal of premalignant tumours as a means of reducing future colorectal cancer risk has been called into question⁸. It would seem appropriate to address this in groups of patients who have a relatively high risk of colorectal cancer. It seems reasonable to assume that the evidence, which does suggest that polypectomy reduces the subsequent colorectal cancer risk in an unselected screening population, would also apply to those with a family history of the disease. Only randomized controlled trials with colorectal cancer mortality as an endpoint can determine whether screening and polypectomy is indeed beneficial. There is certainly a need for such studies but, as highlighted by the King's Fund consensus symposium⁶⁵, polypectomy must continue to be considered an important method of reducing future risk of colorectal cancer.

There is substantial indirect evidence to show that polypectomy is effective in reducing the chance of subsequent colorectal cancer. Epidemiological studies of adenoma and carcinoma prevalence at autopsy suggest that about 10 per cent of tubular adenomas >1 cm in size will become malignant¹, corresponding to an annual conversion rate of three per 100 adenomas⁶⁶. In a follow-up study of the natural history of adenomas <5 mm in diameter, 49 per cent grew in size over 2 years, corresponding to a doubling of total adenoma mass⁶⁷. None of the polyps grew to >5 mm but, because adenomas of >5 mm were excluded from the analysis, it is not clear what these findings mean in terms of larger adenomas, which are of greater clinical interest. Certainly, if the adenoma mass of lesions 1-2 cm or more in diameter also doubles in 2 years, a search for and removal of such lesions should be pursued with vigour. Another study documenting the natural history of untreated polyps of >1 cm demonstrated a cumulative risk of cancer at the site of the original polyp of 2.5, 8 and 24 per cent at 5, 10 and 20 years respectively after original detection for each adenoma⁶⁸. This has been considered reassuring by some authors⁸, but this standpoint seems untenable when one considers that the actuarial risk calculated by Stryker *et al.*⁶⁸ was for each adenoma and that, over a mean follow-up of approximately 9 years, 37 per cent of polyps enlarged, 10 per cent of patients developed an invasive cancer at the site of the polyp, and 5 per cent of patients developed cancer at a site remote from the original polyp. The malignant conversion rate for each polyp must also be taken in the context of the findings of one large pathology series of adenomas of >1 cm in which 50 per cent of patients had only one adenoma, 24 per cent had two, 14 per cent three and 12 per cent four or more¹. Indeed, the number of adenomas per patient has been shown to correlate with increased cancer risk⁶⁹. It is possible to deduce that interruption of the neoplastic process by screening and polypectomy will be effective in reducing malignant change in the colorectum of those screened; the argument against benefit seems hard to sustain in the face of such evidence.

One study of the effect of sigmoidoscopy and polypectomy seems to provide direct evidence demonstrating benefit⁷⁰. The study reported an 85 per cent reduction in the expected incidence of rectosigmoid carcinomas in the screened group. Only polyps within the reach of the rigid sigmoidoscope were removed. This was reflected in the finding of a similar rate of more proximal cancers and this observation was proposed by the authors as an argument against the effect of self-selection bias. However, criticism of this study has been levelled at the exclusion of any individuals who were in any way symptomatic before the study and also the exclusion of 27 cases of cancer diagnosed at the first screen⁷¹. Hence, the expected and observed numbers of cancers in the study group were probably similar. The lack of controls and resultant potential for bias require that the data from this study be interpreted with caution.

Two further studies have attempted to examine the effect of rigid sigmoidoscopy as a simple screening test with removal of

polyps. However, due to various methodological and statistical shortcomings, the data are inconclusive and so the results have been largely discounted^{72,73}. The Kaiser permanent healthcare plan study was a randomized controlled study and is frequently cited as demonstrating benefit for colorectal cancer screening by rigid sigmoidoscopy and polypectomy. The study has been reported and updated on several occasions⁷³⁻⁷⁵ and appears to show a 60 per cent reduction in the colorectal cancer mortality rate⁷⁵. However, the study set out to assess the effects of a 'multiphasic health check-up'. All-cause death was almost identical in screened and control groups, but subanalysis seemed to show benefit in reducing the colorectal cancer mortality rate. The study assessed multiple null hypotheses and so it is not surprising that one or more of the aspects of the check-up might seem to be significantly beneficial. In addition, because the controls also subscribed to the Kaiser permanent health plan, 25 per cent of the controls *versus* 30 per cent of the screened group underwent sigmoidoscopy. The difference in exposure to sigmoidoscopy and polypectomy is insufficient to explain the observed mortality rate benefit, and so the findings are believed to be due to chance or to some unseen bias within the study⁷¹. The authors themselves stated that the results were inconclusive and could not be used as evidence for or against sigmoidoscopic screening⁷³. One further study, the Strang Clinic study⁷², was uncontrolled and, after excluding seven advanced cancers discovered at the initial screen, the 5-year survival rate of the screened group was 88 per cent, higher than the authors would have expected. Again, the lack of formal controls means that various biases could account for the apparent benefit.

The bulk of indirect, circumstantial and uncontrolled evidence strongly suggests that screening and removal of benign neoplasms is beneficial in those with and without a family history. However, a controlled trial is required to address the question formally. It has been calculated that a randomized trial of 14 000 individuals who have a first-degree relative with colorectal cancer would be required to have an 80 per cent chance of detecting a 75 per cent reduction in the colorectal cancer mortality rate⁷⁶. In the meantime, it seems unreasonable to suggest that polypectomy is of no value or inappropriate; it must rather be considered the best weapon against future colorectal cancer risk, as suggested by Williams *et al.*⁷⁷.

Molecular genetics

The field of colorectal cancer molecular genetics has moved on at a breathtaking pace over the past 5 years, and molecular techniques may eventually be employed as another screening method. Much is now known of the somatic molecular events leading to malignancy³⁸. Greater understanding is also coming to the field of constitutional, heritable genetic lesions which may predispose to colorectal cancer. The gene for familial adenomatous polyposis (FAP), known as *APC*, has recently been cloned and sequenced^{78,79} and mutations causing the FAP syndrome identified^{80,81}. Somatic *APC* and *MCC* (a gene very close to *APC* on chromosome 5q21) mutations have been demonstrated in colorectal cancer tissue arising in patients with no known heritable syndrome^{81,82}. Chromosome 5q21 markers, known to be linked to *APC* and *MCC*, have been shown to be linked to a syndrome which does not amount to FAP but does result in small numbers of adenomas and colorectal cancer^{83,84}. The genes involved are almost certainly *APC* and *MCC*. This evidence for genetic linkage, combined with the known somatic mutations in these genes and evidence that clinical features of FAP are relatively common in non-FAP colorectal cancer⁸⁵, strongly suggests that mutations in *APC* and *MCC* could predispose to malignancy in a proportion of patients with apparently common-or-garden colorectal cancer.

It seems likely that there will be genetic heterogeneity with regard to colorectal cancer susceptibility. Hence, genes other than those in 5q21 may be involved. In one large pedigree with a dominant non-FAP colorectal cancer trait, genetic linkage

to the Kidd blood group has been demonstrated⁸⁶. Kidd, and the HNPCC gene with it, has subsequently been assigned⁸⁷ to chromosome 18q, to a region close to a gene that is altered in colorectal cancer tissue, the *DCC* gene⁸⁸. However, there was no evidence for linkage to *DCC* in two other recent studies of HNPCC kindreds⁸⁹ (M.G.D., unpublished data). Genetic heterogeneity raises logistical problems with using molecular genetic markers for increased colorectal cancer risk. Even if it is shown that only a few genes are involved in colorectal cancer susceptibility, several lesions within any one gene could give an effect, as seems to be the case with *APC* lesions that cause FAP. Unless there are particular mutational hotspots within a reasonably small number of genes, it seems unlikely that population screening using molecular analysis would ever be possible. However, it may be possible to screen patients who develop colorectal cancer at a young age for the most common genetic lesions. Relatives of individuals with detectable mutations could then be tested for the same genetic abnormality, and gene carriers screened by colonoscopy. The possibility of prophylactic colectomy may also have to be considered.

Molecular genetics holds much for the future. If it proves possible to identify gene defects predisposing to colorectal cancer, carriers could be screened intensively and trials of dietary intervention or chemoprevention instigated in such a defined high-risk group, thereby avoiding the statistical and methodological problems of previous studies in this field. Understanding the gene structure and function may also eventually lead to a more rational approach to anticancer therapy.

Conclusion

There can be little doubt that a family history of colorectal cancer indicates an increased risk of large bowel malignancy, and all available evidence suggests that the nature of that risk is the inheritance of one or more cancer susceptibility genes. Those at risk can be identified simply on the basis of family history, and molecular genetics may be able to identify at least a proportion of those at very high risk. There is evidence that compliance with screening in such a group would be higher than in population screening programmes⁹⁰. It is interesting to note in the study by Blalock *et al.*⁹⁰ that the improved compliance did not appear to be due to a perception of increased risk. Although there are no large definitive studies, those which are available demonstrate that a higher detection rate of benign and malignant colorectal neoplasms is achieved by screening individuals with a family history than by screening a non-selective group. Although by no means conclusive, all available data point to a benefit for early detection and removal of such colorectal neoplasms.

This paper has explored the case for identifying and screening individuals with a high risk of colorectal cancer. There is a corollary to this discussion. Individuals at high risk due to family history could constitute at least 20 per cent of all cases of colorectal cancer and, overall, relatives of patients with colorectal cancer have a lifetime risk of 11 per cent¹⁹, while a smaller proportion have a 50 per cent risk. Hence it is possible that the balance of the risk-benefit ratio may be tipped such that there may be no justification for screening those who do not have a genetic predisposition. The arguments against population-based screening and the risks associated with it⁹ would be even stronger if the remaining risk of colorectal cancer for those individuals with no predisposition was only slightly lower than for the unselected population currently being assessed in controlled trials. This is exemplified by the calculation of the risks of colonoscopy in screening patients who have undergone previous polypectomy. If the residual risk to a 50-year-old American man is one in 40 and the effectiveness of colonoscopy at 3-year intervals is 100 per cent in preventing colorectal cancer death, 283 colonoscopies would be required to prevent one cancer death, incurring 0.6 colonic perforations

and 0.04 perforation-related deaths²⁰. Hence, screening is 25 times more likely to prevent a cancer death than to cause a death. This level of benefit may be acceptable, but if the residual risk of the screened population is only one in 80 and colonoscopy is 50 per cent effective in preventing cancer death (a more likely estimate than 100 per cent) the benefit becomes even less obvious, as screening would be only six times more likely to prevent a death than to cause one. Although 1131 colonoscopies would be required to prevent one cancer death, there would be 2.3 colonic perforations, 0.17 procedure-related deaths and a cost of \$331 000 (£190 000). Clearly, the colorectal cancer risk to those being screened by invasive screening procedures is crucial to the overall effectiveness of the programme. If the risk to those with no genetic predisposition is low and FOB false positives remain at the same rate, the risks of invasive screening of those with a positive FOB test may indeed outweigh the benefits.

Targeting screening to those at a high risk of colorectal cancer may not only be an effective strategy in itself, but controlled studies in such groups may answer many of the questions on the overall efficacy of polypectomy in reducing future risk of colorectal cancer. This paper has shown that the risk of neoplasia in individuals who have a genetic predisposition to colorectal cancer is so high that even those most vehemently against any form of cancer screening would find the argument against attempts at early detection and removal difficult to sustain.

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Prevention of venous thromboembolism after surgery: a review of enoxaparin

This review discusses the problem of deep vein thrombosis (DVT) after operation and identifies three levels of risk of DVT: low (<10 per cent), moderate (10–40 per cent) and high (40–80 per cent). Special emphasis is placed on the most recent prophylactic treatment, low molecular weight heparins (LMWHs), particularly enoxaparin. Several LMWHs are now available, but they differ slightly and each must be evaluated on its own merits. In general, however, LMWHs are both effective and safe in those patients at moderate or high risk of DVT. Thromboprophylaxis is cost effective when analysed using health-economic methodology.

The main and most serious complication of deep vein thrombosis (DVT) after operation is fatal pulmonary embolism. In the old days 'silent' pulmonary emboli killed patients after an otherwise uneventful postoperative course, perhaps when the patient was about to leave hospital. Even today we meet this killer during necropsies, but it is now considered an avoidable cause of death. The aim of this review is briefly to discuss the problem of thromboembolism after operation and the place of low molecular weight heparins (LMWHs) in prophylaxis, with particular reference to one of them, enoxaparin. This product has recently been licensed for prevention of DVT in the UK. Another LMWH, dalteparin (tedelparin), has also been licensed recently for prophylaxis in the UK.

Different levels of risk in surgery

Patients can, and should, be routinely assessed for thrombotic risk before surgery, using simple clinical variables^{1,2}.

Low-risk patients have a risk of DVT of <10 per cent, a risk of proximal DVT (popliteal or above) of <1 per cent, and a risk of fatal pulmonary embolism of <0.1 per cent. Such patients include those undergoing only minor surgery (<30 min duration), as well as younger patients (aged under 40 years) undergoing major surgery (>30 min duration) who have no risk factors. Prophylaxis in such patients is probably not cost effective and has a low benefit:risk ratio; however, some surgeons would use inexpensive, low-risk methods such as graded elastic compression stockings in low-risk patients. Factors that increase risk, indicating the need for prophylaxis, include previous venous thromboembolism, thrombophilias (deficiencies of antithrombin III, protein C, protein S, or lupus anticoagulant), obesity, malignancy, varicose veins, trauma, lower limb surgery, and prolonged immobility. The risk of modern, low-dose oestrogen oral contraceptives is controversial³.

Moderate-risk patients have a risk of DVT of 10–40 per cent,

a risk of proximal DVT of 1–10 per cent, and a risk of fatal pulmonary embolism of 0.1–1 per cent. Such patients include those undergoing major general, urological, or gynaecological surgery who are aged 40 years or over, as well as those with the above-mentioned risk factors.

High-risk patients have a 40–80 per cent risk of DVT, a 10–25 per cent risk of proximal DVT, and a 1–10 per cent risk of fatal pulmonary embolism. They include patients with major trauma, surgery to the hip, knee or lower limb, those undergoing extensive pelvic or abdominal surgery for malignancy, and those undergoing major surgery with a history of previous thromboembolism or thrombophilia.

Anticoagulant effects and pharmacological promise of low molecular weight heparins

Examining the use of prophylaxis against venous thromboembolism after operation shows great variation between countries, which has less to do with possible differences in epidemiological background than with different attitudes towards the problem among surgeons. Worldwide, the dominant prophylactic method, when one is used, has been low-dose heparin⁴. Its effectiveness in moderate- and high-risk patients is well documented in a number of studies and is summarized in the meta-analysis of Collins *et al.*⁵. Other options are mechanical methods, oral anticoagulants and dextran².

Interest in the development of LMWHs was stimulated by the observation that low molecular weight fractions, prepared by gel filtration from standard heparin, have a different anticoagulant profile from their parent unfractionated heparin^{6,7}. Theoretical hypotheses, based on these findings together with animal experiments, suggested that it might be possible to obtain a good thromboprophylactic effect with low bleeding potential. Today there are several commercially available LMWH fragments differing in molecular weight, production methodology (either chemical or enzymatic depolymerization), and biological and chemical function⁸. The method of preparation *per se* seems to be of minor importance in terms of effect, at least if the molecular weight distributions

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of the products are similar⁹. In one bleeding model, using the gastric mucosa in rats, it has been possible to show differences between LMWHs¹⁰. Thus dalteparin resembles standard heparin in its bleeding pattern, that is, prolonging bleeding time and increasing blood loss. Enoxaparin has to be given in doses five to ten times higher (in anti-Xa units) to elicit a similar degree of bleeding. Turning to clinical effects, however, there is little evidence to indicate that there is a significant difference between the various preparations.

All the LMWHs contain a unique pentasaccharide sequence with specific binding to antithrombin III. Those developed for commercial use have mean molecular weights¹¹ from 4000 to 6500 Da. They have a reduced ability to catalyse the inactivation of thrombin relative to their ability to inhibit factor Xa¹²⁻¹⁴. In platelet-free assay systems, the various commercial LMWHs have antifactor Xa:antifactor IIa ratios of between 4:1 and 2:1 compared with 1:1 for standard heparin. *In vivo*, however, the anticoagulant profile of standard heparin, but not of LMWH, is altered by the presence of platelet factor 4^{13, 15} and by the protection of factor Xa bound to the platelet membrane in the prothrombinase complex^{16, 17}. Since the molecular weight distribution of LMWHs varies between preparations, the anticoagulant profiles are different, and there has been an attempt to use an international LMWH reference standard¹⁸ with a specific activity of 168 anti-Xa units/mg and 68 anti-IIa units/mg.

The plasma recovery and pharmacokinetics differ between LMWHs and standard heparin primarily because of their different binding characteristics to plasma proteins and endothelial cells. From a practical point of view, there are three pharmacodynamic properties which differentiate LMWHs from standard heparin and make them interesting: a better and close to 100 per cent bioavailability after subcutaneous administration, a longer biological half-life, and less variable anticoagulant response to weight-adjusted doses^{19, 20}. LMWHs are cleared from the circulation mainly by the kidneys^{21, 22}.

Today there are altogether some 50 studies which analyse the prophylactic effect of LMWHs; most of them compare the LMWHs with standard low-dose heparin²³⁻²⁶. A few studies are placebo controlled, and there are three comparisons with dextran²⁷⁻³⁵. To summarize, LMWHs are significantly better than placebo or dextran and at least as effective as standard low-dose heparin, both in general and orthopaedic surgery²⁶. In general surgery, there is a relative risk reduction of 21 per cent in favour of LMWHs over standard heparin, and in orthopaedic surgery a relative risk reduction of 17 per cent. Two recent studies on hip arthroplasty have shown a significant reduction of proximal thrombi with LMWH compared with standard low-dose heparin³⁶ or with adjusted low-dose heparin³⁷. This effect also had an influence on scintigraphically detected pulmonary embolism³⁶ but the clinical implication of this is unknown. Concerning fatal pulmonary embolism, available data indicate a very low risk with LMWH, and in randomized comparisons between standard low-dose heparin and LMWHs the compiled frequencies are 0.12 and 0.02 per cent, respectively²⁶.

Based mainly on experimental data, some of the early studies

on LMWH used excessive doses and there was an increased frequency of haemorrhagic complications³⁸⁻⁴⁰. In all recent studies, however, where correct and efficacious doses have been used there has been no increase in tendency to bleed.

Enoxaparin: efficacy and safety

Although it may be difficult to show any clinically relevant differences between the various LMWH preparations⁸, each of them must be evaluated on its own merit. Enoxaparin has a mean molecular weight of 3500-5500 Da and is produced from standard heparin by benzylolation and alkaline depolymerization.

In three consecutive randomized open studies, the optimal prophylactic dose of enoxaparin was investigated in a total of 892 patients undergoing abdominal, gynaecological, thoracic or urological surgery⁴¹. Using the fibrinogen uptake test for diagnosis of DVT, there was no difference in the frequency of DVT between enoxaparin doses of 60, 40 or 20 mg per day. The overall frequency with enoxaparin was 2.7 per cent, *versus* 4.6 per cent with standard low-dose heparin. Bleeding complications did not differ, but in the group receiving highest dose, haematocrit and haemoglobin levels decreased significantly.

To evaluate the antithrombotic efficacy and safety of enoxaparin under normal hospital conditions, a large German multicentre study has been performed in 10032 patients undergoing general, abdominal, gynaecological or urological surgery⁴². Diagnosis of thromboembolic complications was based on clinical features, and suspicious events were verified with lung scintigraphy and phlebography. Based on the results from the dose-ranging study⁴¹ all patients received 20 mg enoxaparin daily. Pulmonary embolism was reported in 24 patients and the frequency of fatal embolism was 0.03 per cent. The frequency of thrombosis was 0.11 per cent; 26 patients (0.26 per cent) died. The follow-up time was only 7 days. The tolerance and safety were excellent.

In elective hip surgery, dose-finding studies have shown the optimal dose to be 40 mg enoxaparin daily, starting some 12 h before surgery⁴³. One study which was placebo controlled²⁸ showed that enoxaparin was significantly more effective, reducing the frequency of DVT from 51.3 to 10.8 per cent. Table 1 summarizes the studies in elective hip surgery where enoxaparin has been compared with other prophylactic treatments. In all studies bilateral ascending phlebography was used for diagnosis of DVT. In the study by Planes *et al.*⁴⁴ and in the Danish study⁴⁶ the first dose was given 12 h before surgery, and in the Canadian study⁴⁵ the first dose was given after surgery, which was also the case in the placebo-controlled trial of Turpie *et al.*²⁸. In abstract form, there is one further investigation supporting the possibility of starting prophylaxis after operation⁴⁷. In the report by Levine *et al.*⁴⁵ there were significantly more bleeding complications in the group receiving standard heparin than in the group receiving enoxaparin; the dose of heparin (7500 units twice daily) was, however, rather higher than usual.

The conclusion from both general surgical and orthopaedic

Table 1 Randomized trials comparing enoxaparin with other types of prophylaxis in total hip replacement

Reference	Year	Prophylaxis	Dose	No. of patients	No. with deep vein thrombosis
Planes <i>et al.</i> ⁴⁴	1988	Enoxaparin	40 mg × 1	124	15 (12)
		Unfractionated heparin	5000 units × 3	113	27 (24)
Levine <i>et al.</i> ⁴⁵	1991	Enoxaparin	30 mg × 2	258	50 (19)
		Unfractionated heparin	7500 units × 2	263	61 (23)
Danish Enoxaparin Study Group ⁴⁶	1991	Enoxaparin	40 mg × 1	108	7 (6)
		Dextran 70	500 ml × 4	111	24 (22)

Values in parentheses are percentages

trials is that enoxaparin is both effective and safe in the prophylaxis of DVT.

Cost effectiveness of thromboprophylaxis in surgery

In recent years, the healthcare sector has increasingly been involved in decision making based on economic calculations. Of the various approaches of handling cost outcome problems, cost-effectiveness analysis is the most simple and is often based on a decision model, the key issue being to compare various strategies. Over the years there has been a number of cost-effectiveness evaluations of thromboprophylaxis⁴⁸⁻⁵⁵. In the study by Bergqvist *et al.*⁵⁶ three prophylactic options were analysed: no prophylaxis with treatment should clinical thromboembolic events occur; general prophylaxis with low-dose heparin in all patients above 40 years of age; and selective treatment based on surveillance after operation with the fibrinogen uptake test. Three types of surgery with different degrees of risk for thromboembolism were compared: cholecystectomy (low), general elective abdominal surgery (moderate) and total hip replacement (high). Real costs for the treatment of thromboembolic and bleeding complications were calculated from a consecutive sample of patients treated at the Department of Surgery, Malmö General Hospital, Sweden. A sensitivity analysis was made with regard to frequency of DVT, prophylactic effect, and treatment costs. Healthcare costs would be minimized with general prophylaxis in groups of patients for whom the frequency of DVT exceeded 8-10 per cent (moderate- and high-risk groups). Selective treatment was always the least satisfactory and the most expensive alternative in all types of surgery. The conclusions from this study are in keeping with those of previous reports, namely that thromboprophylaxis is cost effective. Thus, besides saving lives by preventing fatal pulmonary embolism, it also saves money for society. So far no studies have analysed the cost effectiveness of LMWHs, but as has been indicated above, there is no reason to believe that the conclusions should be any different.

Conclusions

This review has briefly highlighted the problem of venous thromboembolism after operation and has focused on the most recent prophylactic treatment, LMWHs. There are several of these compounds in existence but they are somewhat different in nature and each should be evaluated on its own merits. In general, LMWHs have been found to be both effective and safe in moderate-risk as well as in high-risk surgery; moreover, thromboprophylaxis is cost effective when analysed with health-economic methodology.

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Mechanism of action of external compression on venous function

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Compression stockings and bandages have been shown to improve venous haemodynamics and may act by reducing venous reflux. The aim of this study was to assess the mechanism of action of compression therapy on venous function and to determine whether such treatment may correct valvular incompetence. Both lower limbs of 36 patients (median age 59 (interquartile range 45–65) years) were assessed by duplex ultrasonographic scanning. There were 17 limbs with popliteal vein reflux, 19 with long saphenous vein (LSV) reflux and 21 with short saphenous vein (SSV) reflux. A water-filled adjustable pressure cuff was applied around the knee and inflated gradually, while continuously assessing the veins for reflux using ultrasonographic imaging. The external pressure applied by the cuff was noted when reflux was abolished or when the vein was completely occluded. In four (24 per cent) of 17 popliteal veins, eight (42 per cent) of 19 LSVs and three (14 per cent) of 21 SSVs reflux was abolished before occlusion of the vein. The cuff pressures required to achieve restoration of valvular function were significantly lower than those required to occlude the veins. It is possible, in some refluxing veins, to correct valvular dysfunction by external compression therapy. Coaptation of valvular cuffs to restore valvular competence may be the mechanism of action of compression therapy in venous disease.

External compression therapy has been used in the treatment of venous disease since the times of Hippocrates¹. More recently, the indications for its use have been better defined and the availability of graduated compression stockings has promoted patient acceptability. There remains considerable controversy over the mechanisms of action of external compression therapy despite the widespread acceptance of the benefits of this form of treatment.

Consistent objective demonstration of the effects of external compression on venous haemodynamics has proved elusive. Various types of investigation have been used to assess muscle pump efficiency and venous reflux, with varying results. In normal volunteers, Sigel and colleagues showed an enhancement of femoral vein blood flow in limbs with external compression and demonstrated that this was maintained for up to 30 min after removal of the compression^{2,3}. Using phlebography, other authors have demonstrated improved clearance rates of contrast from the deep veins and a diversion of contrast from the superficial to the deep veins with a reduction in vein diameter^{4,5}. Gjores and Theulesius used foot volumetry to show a reduction in limb volume and a 50 per cent reduction in venous reflux in postphlebotic limbs⁶. The improvement in ejection volume, refilling rates and refilling times, measured using foot volumetry, was confirmed by Jones *et al.*⁷ who went on to show that external compression improved clearance of subcutaneous injections of ²⁴Na. Improved refilling times were also demonstrated by Evander *et al.*⁸ using photoplethysmography. In 1987, Christopoulos *et al.* using air plethysmography and superficial venous pressure measurements showed a reduction in venous reflux with an improvement in ejection fraction in limbs with superficial or deep vein incompetence; they confirmed these findings by demonstrating a reduction in the ambulatory venous pressure in both groups when external elastic compression was applied⁹. This led them to conclude that elastic stockings act by reducing

reflux and improving efficiency of the calf muscle pump. In contrast, although Partsch showed an increase in the expelled volume using foot volumetry, he was unable to demonstrate an improvement in venous refilling times or refilling rates¹⁰. Somerville *et al.* were able to demonstrate an improvement in ambulatory venous pressure, but only after the external compression had been applied for 1 month¹¹. Husni *et al.* discovered that the ambulatory venous pressure was made worse by the application of graduated stockings in postphlebotic limbs⁵. O'Donnell *et al.* were also unable to demonstrate any difference in the resting or ambulatory venous pressures but found the systolic venous pressure to be halved with the application of a graduated stocking¹².

These varying results may be due to differences in the method and application of external compression, the variety of tests used to define venous function, and to unsatisfactory subgrouping of a heterogeneous patient population. The development of a sophisticated non-invasive test, duplex ultrasonographic scanning, allows some of these problems to be avoided. The aim of this study was to determine the effect of external circumferential pressure on venous reflux within the deep and superficial veins of the lower limb, using duplex ultrasonography.

Patients and methods

Patients were assessed clinically and by duplex scanning to determine the site of venous reflux in the lower limbs. The duplex scanner also allowed colour flow mapping of the Doppler signal. Imaging was undertaken with the patient standing, taking his or her weight on the limb opposite that being examined. This ensured that the veins were full and enabled the test for reflux to be performed with ease and reliability. Reflux was defined as reverse flow in a vein lasting >0.5 s following the release of manual calf compression. All scans were performed by the same experienced venous ultrasonographer (S.S.). The popliteal vein, the long saphenous vein (LSV) and the short saphenous vein (SSV) at the level of the knee were assessed. All limbs found to have reflux in more than one of these veins, or no reflux in any vein, were excluded from the study. In all, 57 limbs in 36 patients were suitable for inclusion and all patients gave informed consent to the procedure.

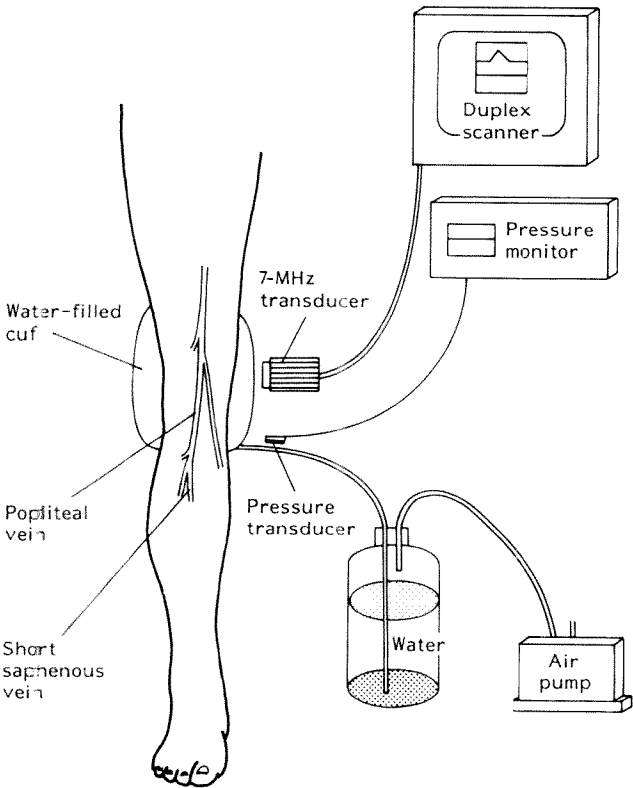


Figure 1 Apparatus used to image the venous system and determine the presence or absence of reflux while applying variable external compression to the leg

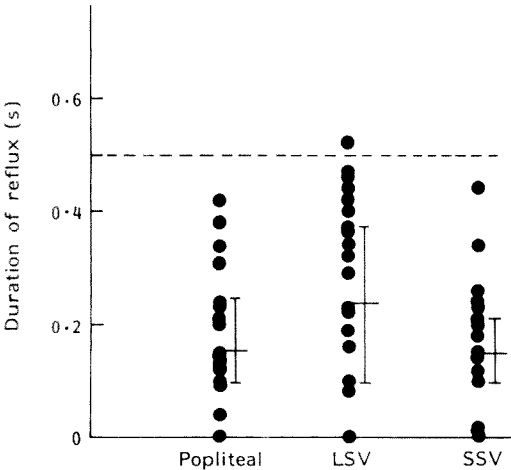


Figure 2 Duration of reflux following the release of manual calf compression in the popliteal vein, long saphenous vein (LSV) and short saphenous vein (SSV) in 20 limbs of ten subjects with no history or clinical evidence of venous disease. Bars are median (interquartile range). Dotted line indicates reverse flow of 0.5 s

The effect of compression on incompetent veins was assessed. A 20-cm wide water-filled cuff with an attached pressure transducer was applied around the knee of the standing patient (Figure 1). Knee level was chosen for a number of reasons. First, most forms of compression therapy compress the limb up to the level of the lower thigh. Second, all three vessels are clearly visible at this level by duplex scanning. Third, the fact that reflux could be identified in these vessels meant that the valves at this level were incompetent. Finally, the effect of compression on valvular function could be readily identified as venous valves are situated at 2–5-cm intervals along these vessels. A specially constructed air-valve system allowed pressures between 0 and 150 mmHg to be applied. The LSV, SSV or popliteal vein was scanned through the cuff at 0 mmHg and reflux confirmed. The diameter of the vein was measured 1 cm above the popliteal skin crease for the LSV

and popliteal vein and 1 cm below the saphenopopliteal junction for the SSV. The cuff was then inflated at the rate of 10 mmHg every 30 s and reflux reassessed in the vein by applying manual calf compression after each pressure increment. The presence or absence of reflux at 40 mmHg was determined and the diameter of the vein being examined was measured at this external pressure. This pressure was chosen as it was the highest conceivable that a commercially available stocking might exert at the level of the knee. The procedure was repeated, with increasing cuff pressure, until reflux in the vein was completely prevented. The cuff pressure required to prevent reflux and the diameter of the vein at this pressure were noted.

The popliteal vein, LSV and SSV in six limbs of three normal subjects were compressed to measure the occlusion pressure. To assess reproducibility the test was repeated on five different occasions. The coefficient of variation was 8 per cent.

The diameters of the popliteal vein, LSV and SSV were measured in both limbs of a further series of ten patients without clinical evidence of venous disease in either leg. The diameters were measured through the cuff at 0 mmHg using the same landmarks as previously described. In addition, the degree of reflux was assessed on the basis of duration of reverse flow following the release of manual calf compression. The duration of reverse flow following this procedure was measured in the popliteal, LSV and SSV of these 20 clinically normal lower limbs. Only one of the 60 veins examined had reverse flow of >0.5 s (Figure 2). In common with other authors, we have found this method to be reliable in the detection of reflux in veins^{13–15}.

Results

Thirty-six patients, 19 men and 17 women, were included in the study. There were 17 limbs in 12 patients (median age 63 (interquartile range (i.q.r.) 46–67) years) with only popliteal vein reflux, 19 limbs in 12 patients (median age 49 (i.q.r. 43–65) years) with only LSV reflux, and 21 limbs in 15 patients (median age 60 (i.q.r. 45–67) years) with only SSV reflux on duplex scanning. There were 15 limbs in which either no venous abnormality was found or in which reflux was present in more than one vein.

Figure 3 shows the diameters of the incompetent veins compared with the diameters of the three vessels in 20 normal limbs of ten patients, five men and five women, of median age 54 (i.q.r. 45–64) years. The diameter of incompetent veins was greater than that of normal vessels at the three anatomical sites examined.

Figure 4 shows the diameters and pressures required to abolish reflux in the three vessels. Reflux was abolished without occluding the vein in four (24 per cent) of the popliteal veins, eight (42 per cent) of the LSVs and three (14 per cent) of the SSVs. The vein diameter at which reflux was abolished was significantly less than the vessel diameter at a cuff pressure of 0 mmHg in all three vessels. The cuff pressure required to occlude the vessels was similar in all three vessels; it was

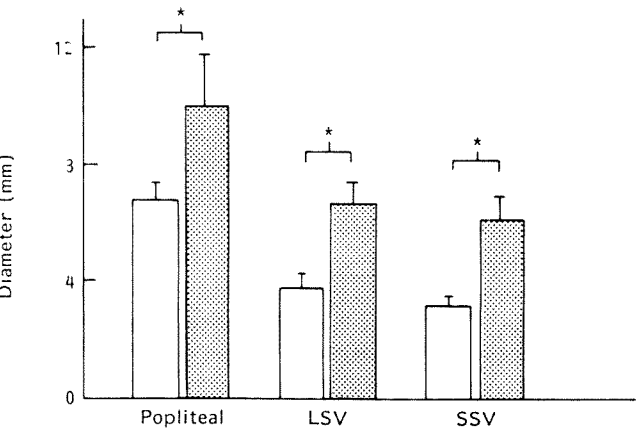


Figure 3 Comparison of veins with demonstrable reflux (shaded bars) and normal (white bars). Values are mean (s.d.). LSV, long saphenous vein; SSV, short saphenous vein. *P < 0.01 (Wilcoxon rank sum test for unpaired samples)

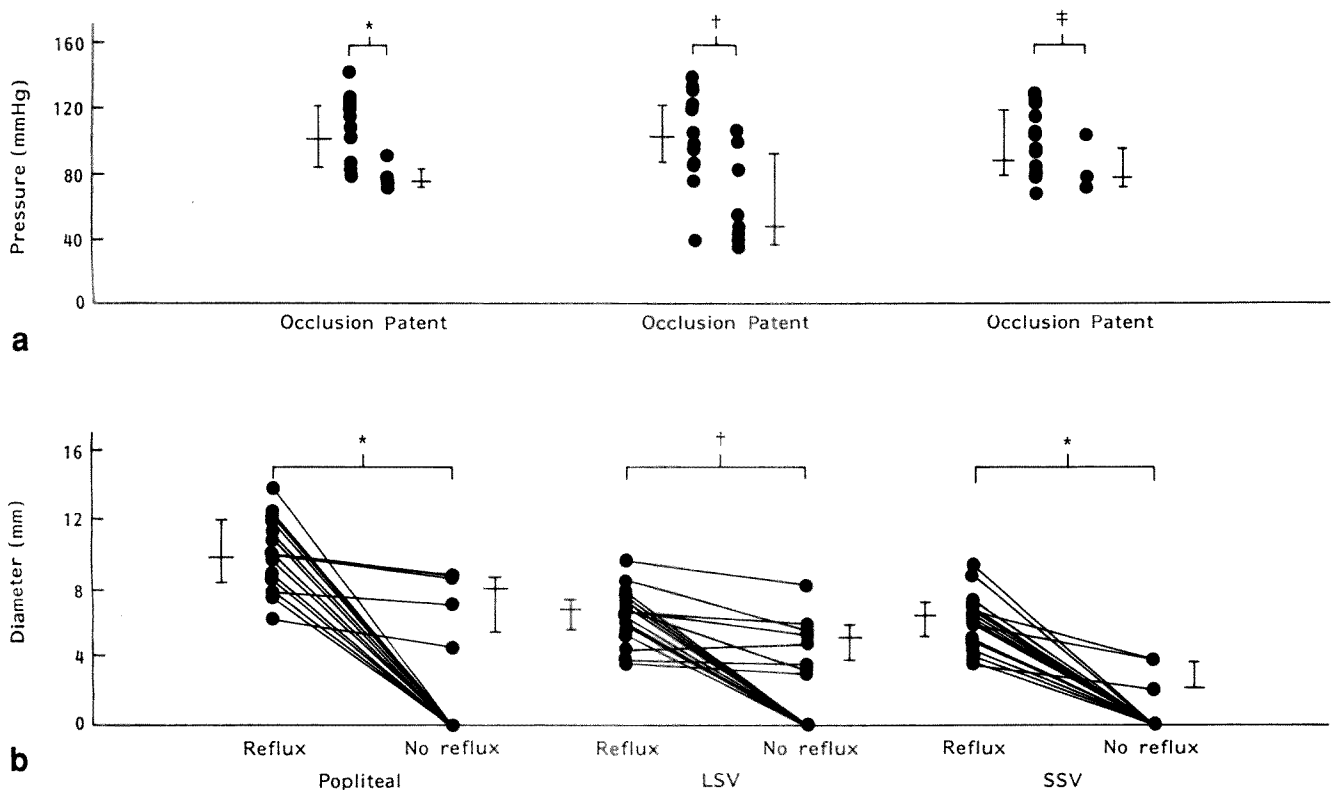


Figure 4 a Pressures and b diameters required to abolish reflux in veins incompetent at 0 mmHg external compression pressure. Bars are median (interquartile range). LSV, long saphenous vein; SSV, short saphenous vein. Reflux was abolished while some veins were still patent; in others, reflux was abolished only after complete vein occlusion. * $P < 0.05$; † $P < 0.01$; ‡ P not significant (Wilcoxon rank sum test for unpaired samples)

Table 1 Diameters of vessels at 0 and at 40 mmHg external pressure, with those still demonstrating reflux distinguished from those that did not

	Popliteal vein		Long saphenous vein		Short saphenous vein	
	No.	Median diameter (mm)	No.	Median diameter (mm)	No.	Median diameter (mm)
All refluxing vessels at 0 mmHg ($n = 57$)	17	10 (7.8–10.8)†	19	6.7 (5.3–7.0)*†	21	6.1 (4.9–6.8)‡
Reflux abolished at 40 mmHg ($n = 5$)	0	—	5	3.8 (3.4–4.8)	0	—
Reflux not abolished at 40 mmHg ($n = 52$)	17	9 (7.0–10.0)	14	5.8 (5.0–6.4)	21	4.6 (3.9–5.9)

Values in parentheses are interquartile ranges. * $P < 0.01$ (all refluxing vessels versus reflux abolished); † $P < 0.05$ (all refluxing vessels versus reflux not abolished); ‡ P not significant (all refluxing vessels versus reflux not abolished); all comparisons, Wilcoxon rank sum test for unpaired samples

significantly more than the pressure at which reflux was abolished without occlusion in all but the SSVs. Eight of the 17 popliteal veins had ultrasonographic appearances suggesting past thrombosis; in only one of the eight was reflux abolished before occlusion, whereas in three of the remaining nine reflux was abolished before the vein occluded.

Table 1 shows that none of the popliteal or SSVs became competent at an external compression pressure of 40 mmHg. On the other hand, five of the 19 LSVs stopped refluxing at this pressure. All the vessels except the SSVs showed a statistically significant reduction in diameter when the cuff pressure was 40 mmHg. No vein was occluded at this pressure.

Discussion

Previous studies have addressed the effect of compression stockings on venous function. Many hypotheses have been advanced to explain the beneficial effect of stockings, including diversion of blood from the superficial to the deep systems, prevention of high amplitude pressure swings in the superficial veins during systole, 'support' of the superficial veins,

enhancement of compression and emptying of deep veins, and reduction in diameter of veins with restoration of competence^{2–12}. The proposed mechanisms suggest either an improvement in calf muscle pump function or a reduction in venous reflux.

Both of these mechanisms depend on the integrity of the venous valvular system, the function of which is now best examined using duplex scanning^{16,17}. Although it would have been desirable to examine valvular morphology, this is not possible with duplex scanning. The larger valves (e.g. at the saphenofemoral junction or the popliteal vein) are occasionally seen on duplex ultrasonography but their morphology is not a reliable determinant of function (S.S. and P.D.C.S., personal observation). The presence or absence of reflux within the vein was therefore used as a qualitative measure of valvular function. The effect of external compression was assessed using a water-filled cuff, a device determined by the need to vary the applied pressure while allowing ultrasonographic imaging of the veins. All three vessels were examined at the knee. Since the hydrostatic column between the right atrium and the knee was the same for all three veins, the close correlation between

the occlusion pressures for all three veins suggests that even distribution of pressure was achieved within the leg. The water-filled cuff system also provided clear real-time ultrasonographic images with little loss of resolution in the colour mode.

External compression abolished signs of reflux in 15 of the 57 veins examined. It was not possible to examine the precise haemodynamics just before occlusion of the vein with the limitations of the methodology. The vein under examination loses relatively little of its diameter for large changes in external pressure due to the non-linear pressure-vein diameter relationship, particularly when the external pressure is low. However, the reverse is true just before occlusion, when a small change in pressure results in a large change in vessel diameter¹⁸. While it may be possible to restore competence in a greater proportion of veins with reflux at or near the occlusion pressure, it was not possible to demonstrate this effect. In the few veins in which competence was restored before occlusion, the pressure required was significantly lower than the occlusion pressure in all but the SSV group. This suggests that the initial, relatively small change in diameter produced by a low cuff pressure is sufficient to restore valvular competence in those veins in which external compression prevents reflux. The large change in diameter at or near the occlusion pressure is unlikely to contribute to the prevention of reflux in the clinical context.

An indication that restoration of valvular competence may be achieved with sufficient reduction in vein diameter comes from data on indirect valvuloplasty. This is a technique to restore competence to a deep venous valve and involves the use of a Dacron (Du Pont, Stevenage, UK) cuff wrapped around the vein, the diameter of the cuff being adjusted until competence is restored^{19,20}. The mechanism of action of the cuff is thought to be to allow the valve cusps to appose more efficiently. Though long-term patency and competence rates are not available, intraoperative tests indicate that valvular function could be restored in all veins. One reason for the success of this procedure compared with the present external compression results may lie in the selection of patients; in this study eight of the 17 popliteal veins were incompetent secondary to previous thrombotic disease, whereas the patients who underwent indirect valvuloplasty had mostly primary deep vein valve failure. Furthermore, the mechanisms are different; a Dacron wrap prevents dilatation of the valve ring regardless of the transmural pressure changes while external compression allows changes in vein diameter reflecting transmural pressure differences.

This study has shown that external compression restores valvular competence in a proportion of cases, both in the superficial and deep venous systems. This effect is directly associated with a decreased vein diameter, lending support to the concept that external compression allows valve cusps to appose and so restores competence. However, the external pressure required to achieve restoration of competence was far higher than that produced by grade 3 stockings at the knee. Measurement at an external cuff pressure of 40 mmHg confirmed that in five veins (9 per cent) competence was restored, compared with the total of 15 (26 per cent) which became competent before complete occlusion. However, simple comparison with graduated compression stockings may not be appropriate because while static pressure achieved at the knee by stockings is much lower than the pressure required in this

study, dynamic pressure with stockings (e.g. with the patient walking) may be higher. Also, the effect of compression on valvular function has been assessed with compression only at the knee; it is possible that external compression from ankle to knee restores competence in a larger number of veins, thereby improving venous function in a greater proportion of limbs.

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Angioscope-guided neodymium yttrium–aluminium–garnet laser valvulotomy for *in situ* vein bypass

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Non-reversed *in situ* vein bypass is the preferred method for below-knee and tibial revascularization^{1–3}. However, despite the theoretical advantages of *in situ* bypass, patency rates are not significantly different from those of reversed vein bypasses⁴. In an effort to improve the technique of valvulotomy, an experimental study of laser valvulotomy with angioscopic guidance was designed. A 400- μ m fibre and a 2-mm hot-tip laser probe were examined and results compared with those from conventional valvulotomy.

Materials and methods

Cadaveric long saphenous vein segments from 46 adults below the age of 65 years were harvested in the autopsy room. The specimens were stored in buffered saline solution and used on the same day for the experiments. Vein segments 20 cm long, containing two valves each, were transferred into a Perspex box. Within this the vein was mounted on two adjustable blocks. The distal vein orifice was sutured to a metal ring on one of the blocks, keeping the lumen open to accept instruments. A continuous infusion of buffered saline was connected to the proximal end to distend the valve cusps and to cool the tissue during laser valvulotomy. An Olympus BF-P 3C10 bronchoscope (Olympus Optical, Hamburg, Germany) was used to position the laser probe and allow macroscopic assessment of valvulotomy.

Three groups were investigated. Group 1 involved valvulotomy with a commercially available standard valvulotome (Insitucat; Braun, Melsungen, Germany). A range of differently sized valvulotomes was used in a manner recommended by the manufacturer. The procedure was considered as complete when free passage of the valvulotome was achieved and angioscopy confirmed that all valve cusps had been destroyed.

In group 2, a 400- μ m fibre was connected to a neodymium yttrium–aluminium–garnet (NdYAG) laser (Medilas; MBB, Otto-brunn, Germany) with a power of 20 W. The fibre was advanced through the instrument channel of the angioscope. Each valve cusp was identified with the angioscope and the laser probe was placed perpendicular to the cusp. A series of laser pulses with a duration of 0.2 s and a pause of 0.3 s was transmitted to each valve cusp until complete valvulotomy was confirmed by angioscopy.

In group 3, a 300- μ m fibre with a 2-mm diameter PLR plus (MBB) hot-tip biocompatible metal cup was connected to the angioscope. Owing to the size of the hot-tip, the probe could not be passed through the instrument channel, but was mounted on to the outside of the angioscope. Laser valvulotomy was performed as described for group 2.

The valve areas of each vein segment were excised after completion

Valvulotomy for in situ vein bypass is commonly performed with a valvulotome. Although the procedure can be controlled through an angioscope, the dangers of intimal damage and valve remnants remain. An experimental study was designed to evaluate angioscopic laser valvulotomy compared with standard mechanical valvulotomy (n = 16). Two different laser probes, a bare 400- μ m fibre (n = 20) and a 2-mm hot-tip (n = 26) were tested. Results were investigated by histology and scanning electron microscopy. Hot-tip laser valvulotomy achieved significantly better results than the 400- μ m fibre. The Insitucat valvulotome yielded the worst results, with valve remnants in all cases and an 88 per cent rate of intimal damage. It is concluded that laser valvulotomy can be performed simply and safely with a very low incidence of valve remnants and intimal damage.

of valvulotomy. One valve area was stored in formaldehyde for histology after staining with haematoxylin–eosin and van Gieson stains. The criteria for histological assessment were endothelial damage, valve remnants and adventitial damage, i.e. perforation. The other valve area was excised and stored in buffered glutaraldehyde for scanning electron microscopy of valve remnants and endothelial damage. Statistical analysis was carried out using the χ^2 test⁵.

Results

Histology results are given in Table 1. The hot-tip valvulotome proved to be the most efficient and least damaging method. In particular, no perforation of the vessel wall was observed. Scanning electron microscopy confirmed these results (Table 2). Except for perforations, statistical significance was achieved for all histological and electron microscopic criteria testing the hot-tip against the valvulotome. The hot-tip caused significantly less endothelial damage than the 400- μ m fibre (electron microscopy, $P < 0.001$; histology, $P < 0.05$) and left fewer valve remnants (electron microscopy, $P < 0.01$; histology, $P = 0.4$). The incidence of perforations was not significantly different. The 400- μ m fibre was significantly superior to conventional valvulotomy with respect to valve remnants (electron microscopy, $P < 0.01$; histology, $P < 0.0001$).

Table 1 Histological assessment

	Valvulotome (n = 16)	400- μ m Fibre (n = 20)	Hot-tip laser (n = 26)
Endothelial lesions	14	12	7*
Valve remnants	16	6†	4†
Perforations	0	2	0

* $P < 0.001$ (hot-tip versus valvulotome, χ^2 test); † $P < 0.0001$ (400- μ m fibre and hot-tip versus valvulotome, χ^2 test)

Table 2 Electron microscopic assessment

	Valvulotome (n = 16)	400- μ m Fibre (n = 20)	Hot-tip laser (n = 26)
Endothelial lesions	14	17	8†
Valve remnants	16	12*	6‡

* $P < 0.01$ (400- μ m fibre versus valvulotome, χ^2 test); † $P < 0.001$; ‡ $P < 0.0001$ (both hot-tip versus valvulotome, χ^2 test)

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Discussion

This is the first experimental study to compare conventional valvulotomy with angioscope-guided laser valvulotomy of human long saphenous vein segments. It shows that valvulotomy using a hot-tip laser produces significantly less endothelial damage and leaves significantly fewer valve remnants than the Insitucat. However, the other laser probe tested (the bare 400- μ m fibre) yielded less convincing results. Although it was more efficient in excising valves than the conventional valvulotome, it produced just as much endothelial damage and, even worse, it caused perforation in two cases. This finding was not statistically significant, probably because of the small numbers involved.

In an animal experiment, White *et al.*⁶ used a 12-W argon laser *in vivo* with a specially designed 'valvulase' tip. They observed a 45 per cent perforation rate with a bigger 2-mm probe and no full-thickness lesions with a smaller probe. The hot-tip with a 2-mm diameter used in the present study proved equally successful. To avoid damage to the endothelium, correct angioscopic positioning and effective cooling with continuous infusion from the proximal end are crucial. Additional infusion of saline through the perfusion channel of the angioscope is probably required *in situ* to clear the field of view of blood. The laser probe may be advanced through the instrument channel of the angioscope or it may be fixed to the outside of the instrument, depending on the diameter of the probe and the angioscope. We found transangioscopic positioning easier to achieve. With a little practice it is possible to meet the demand for exact positioning of the laser probe. It is equally important to adjust the laser power and the pulse interval so that neither incomplete valve destruction nor thermal injury to the adjacent tissues occurs. In the present system the power of 20 W with a 0.2-s impulse and a 0.3-s pause appeared optimal. The use of an angioscope during vein preparation for the *in situ* technique has the additional advantage that tributaries to the vein can be identified⁷. The light of the angioscope shining through the skin allows one to perform ligation of the tributaries through small skin incisions, with obvious advantages⁷.

Complete valvulotomy for *in situ* bypass is important. Karino proved that valve remnants cause whirls with a consequent low flow velocity, sedimentation and aggregation of blood cells⁸. The streams of low velocity in the pockets of valve remnants may cause hypoxic damage to thrombocytes and induce thrombus formation⁹. The other risk of valvulotomy, an intimal lesion, is probably even more important. Thrombus formation by activation of the clotting

cascade following endothelial injury is well documented¹⁰. No matter how successful the results of *in situ* bypass may be, early thrombosis is not uncommon¹¹ and endothelial damage during preparation and valvulotomy is a probable explanation. Theoretical advantages of the *in situ* technique over reversed vein bypass, such as better size match of the proximal and distal anastomosis due to the conical shape of the long saphenous vein and the preservation of the vasa vasorum in the venous bed, do not seem to produce better patency rates^{2,4}. A possible explanation may be late sequelae from valve remnants and intimal damage. Laser valvulotomy with the hot-tip NdYAG laser yielded perfect results in more than 70 per cent of cases compared with none for conventional valvulotomy. A primary prerequisite for successful *in situ* bypass may thus be met with this method.

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Dermatan sulphate: a safe approach to prevention of postoperative deep vein thrombosis

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To assess the efficacy and safety of dermatan sulphate (MF 701) in preventing postoperative deep vein thrombosis (DVT), 324 patients aged 40 years or over undergoing elective major general surgical operations were included in a randomized trial comparing MF 701 (100 mg intramuscularly once a day) with unfractionated calcium heparin (UFH, 5000 units subcutaneously three times daily). Both treatments were initiated before operation and continued until discharge. In all, 316 patients were included in the analysis (MF 701, 157; UFH, 159). Serial impedance plethysmography was performed in all patients; a ¹²⁵I-radiolabelled fibrinogen uptake test was added to impedance plethysmography in a randomized subsample of 62 patients (MF 701, 28; UFH, 34). Positivity in either test was confirmed where possible by venography. DVT was diagnosed by venography or, when this could not be performed, by positivity of either impedance plethysmography or fibrinogen uptake test. The incidence of DVT was 3.1 per cent (patients receiving MF 701) and 1.6 per cent (those receiving UFH) in patients undergoing impedance plethysmography alone, and 7.1 and 11.8 per cent, respectively, in those undergoing both impedance plethysmography and fibrinogen uptake test; in neither case was the difference between treatments statistically significant. There were five in-hospital deaths, two in patients receiving MF 701 and three in patients on UFH. The incidence of clinically overt haemorrhage was 5.7 per cent in patients on MF 701 and 17.6 per cent in those on UFH ($P < 0.01$). Postoperative transfusions and reoperations due to bleeding were significantly less frequent in patients receiving MF 701. Mortality rates at 3 months were similar for the two treatment groups. Compared with standard prophylaxis using UFH, MF 701 showed a similar efficacy with a significantly greater safety.

All forms of anticoagulant prophylaxis of postoperative deep vein thrombosis (DVT) entail a risk of haemorrhage which has limited their widespread use in surgical practice¹. Unfractionated calcium heparin (UFH), in low subcutaneous doses, is the drug of choice for preventing DVT after general surgery²⁻⁴, although it causes a consistent increase of approximately 60 per cent in the risk of excessive bleeding⁴ and occasionally serious haemorrhage^{2,5-7}. The recently introduced low molecular weight heparins have practical advantages over UFH but have not been shown to be less haemorrhagic in patients undergoing general surgery⁸⁻¹¹.

Dermatan sulphate (MF 701; Mediolanum Farmaceutici, Milan, Italy) is a natural glycosaminoglycan which potentiates heparin cofactor II and, unlike heparin, does not interact with antithrombin III. Heparin cofactor II is a selective inhibitor of thrombin, so that in the coagulation system dermatan sulphate acts as a pure antithrombin agent¹². Studies in animal models indicate that dermatan sulphate is an effective antithrombotic agent¹³⁻¹⁶ and is less haemorrhagic than UFH at equivalent antithrombotic doses¹³⁻¹⁵. The half-life of dermatan sulphate, administered subcutaneously (s.c.) or intramuscularly (i.m.) to humans, is longer than that of UFH^{17,18}, suggesting the possibility of a once-a-day administration regimen.

A controlled clinical trial was performed, aimed at assessing the efficacy and safety of dermatan sulphate in the prophylaxis of DVT after major general surgery. Once-a-day MF 701 was

compared with a standard UFH regimen in a prospective, randomized study.

Patients and methods

Patients

Patients aged 40 years or over, scheduled for elective abdominal, thoracic or breast surgery lasting >30 min, and giving their consent after a thorough explanation of the investigation procedures, were eligible for the study. Exclusion criteria were as follows: high bleeding risk (prothrombin activity <50 per cent of control plasma, or platelet count <100 × 10⁹ litre, or history of severe bleeding in the past 6 months); kidney failure (serum creatinine >177 μmol/l); abnormal impedance plethysmography on admission; expected hospital stay <7 days after operation; known hypersensitivity to heparin, iodine or contrast media; ongoing anticoagulant treatment; pregnancy. Care was taken to ensure consecutive patient recruitment; a record was kept of excluded patients. The investigation was approved by the ethics committee of Padua University Hospital.

Treatment and study design

MF 701 was provided in 100 mg/2 ml ampoules. MF 701 is extracted from porcine intestinal mucosa; its molecular weight is 27-37 kDa, SO₄:COOH ratio between 1:1 and 1.3:1. It has an anti-IIa activity of 2 units/mg and no detectable anti-Xa activity, when using appropriate chromogenic assays and UFH as a standard. UFH calcium salt was provided in 5000 units/0.2 ml ampoules (Croneparina; Mediolanum Farmaceutici).

Patients were allocated to either serial impedance plethysmography or impedance plethysmography and ^{125}I -radiolabelled fibrinogen uptake test for DVT surveillance and to either MF 701 or UFH according to a computer-generated randomization list with a factorial arrangement. Randomization ratios were 4:1 for the surveillance method (four impedance plethysmography, one impedance plethysmography and fibrinogen uptake test) and 1:1 for the treatment. Patient allocation was performed by opening a sealed envelope after each patient was admitted to the study.

MF 701 was injected i.m. in a dose of 100 mg, 2 h before surgery and then every morning. UFH was injected s.c. at a dose of 5000 units, 2 h before and 12 h after operation, and then three times a day every day. Both treatments were continued until discharge from the surgical department, with this time ranging from 7 to 21 days after operation. No concomitant antiplatelet or anticoagulant drugs were used throughout the study. A standard policy was followed for all patients with regard to mobilization after operation.

Criteria for efficacy

All patients underwent impedance plethysmography on admission, on day 1 after operation and every third (plus or minus one) day throughout the duration of the treatment. Impedance plethysmography equipment and technique used were as previously described¹⁹. The fibrinogen uptake test was added to impedance plethysmography in a patient subgroup. After thyroid blocking by NaI or KI, 100 μCi (3.7 MBq) ^{125}I -radiolabelled fibrinogen (Amersham International, Amersham, UK) was injected immediately after surgery. Leg scans were performed on days 1, 3, 5 and 7 after operation; if there was an increase in uptake, measurements were repeated daily. Criteria for the positivity of the fibrinogen uptake test were those described by Kakkar²⁰. Positivity of either impedance plethysmography or the fibrinogen uptake test was confirmed whenever possible by venography. Symptoms and signs of DVT were also to be investigated by venography performed according to the technique of Rabinov and Paulin²¹; DVT was diagnosed if the venogram revealed a constant intraluminal filling defect.

In the case of clinically suspected pulmonary embolism, a diagnostic algorithm was to be applied as suggested by Hirsh *et al.*²². In-hospital deaths were documented with all the available clinical, laboratory and autopsy information.

Telephone follow-up was undertaken 3 months after hospital discharge to ascertain the status of the patient and whether there had been any hospital admission for a thromboembolic event.

The primary study outcome was venographically proven DVT or, when venography could not be performed, positivity of either impedance plethysmography or fibrinogen uptake test. Secondary outcomes were symptomatic venous thromboembolism and death from any cause, both in-hospital and during follow-up. All impedance plethysmography tracings, fibrinogen uptake test data sheets and venograms were reviewed in blind conditions by three investigators not involved in the management of the patients. The telephone follow-up was also performed on a blind basis.

Criteria for safety

Patients were examined daily for bleeding and any other adverse event. Intraoperative bleeding was assessed according to the surgeon's opinion and the blood transfusion requirement. After surgery, clinically overt bleeding, reoperation due to bleeding, and blood transfusions were recorded until discharge. Bleeding episodes from the intervention site or from an extraoperative source were classified accordingly.

Haemoglobin, haematocrit and platelet count were recorded on admission and then repeatedly until day 7 after operation. Routine serum biochemistry tests were performed on admission and on day 7 after operation.

'Ex vivo' drug monitoring

The activated partial thromboplastin time was determined on admission and on days 3 and 7 after operation. Plasma concentrations of dermatan sulphate were assayed in a subgroup of patients given MF 701 using a kit (Stachrom DS; Diagnostica STAGO, Franconville, France), based on the chromogenic method of Dupouy *et al.*²³, when it became available during the course of the study. For this assay blood samples were taken 4 h after injection on days 1 and 6, 7 or 8 after operation.

Statistics

The study hypothesis was that MF 701 would be as effective as UFH in the prophylaxis of DVT. The DVT rate with UFH was assumed to be 4 per cent, taking into account the relative sensitivities of the two surveillance methods and the respective subgroup sizes. The sample

size was such that an increase in DVT rate to 9 per cent or more for patients on MF 701 would be statistically significant, with an α value of 0.05 (one-sided) and a statistical power of 75 per cent. Using the formula of Makuch and Simon²⁴, 165 patients per group were required.

All the patients meeting the study eligibility criteria were included in the analysis, regardless of minor protocol violations. Patients entering the study despite being ineligible were excluded from analysis but information on their clinical outcome was recorded.

Statistical analysis was performed by an independent statistician using BMDP software (Los Angeles, California, USA). Frequency data were compared by Pearson's χ^2 or Fisher's exact test (both two-sided) and by calculating the 95 per cent confidence interval of the observed differences between groups. Parametric data were compared by one-way analysis of variance (ANOVA), or by ANOVA for repeated measures when appropriate, and expressed as mean (s.d.). Descriptive data and DVT incidence were analysed separately for the four subgroups defined by DVT surveillance method and treatment; clinical outcomes and safety data were analysed according to the treatment.

Results

Patient sample

From January 1987 to December 1989, 406 consecutive patients meeting the criteria for age and type of elective surgery were considered for inclusion in the study, of whom 76 were excluded for the following reasons: prothrombin activity or platelet count below the specified limits (28 and 16 patients respectively); refused consent (eight); abnormal or impossible impedance plethysmography (four); recent bleeding (three); kidney failure (two); ongoing anticoagulant treatment (two); hypersensitivity to iodine (one); short hospital stay (one); logistical and administrative problems (11). Of 330 patients randomized, six had their operations cancelled and eight were excluded from analysis with positive impedance plethysmography (two patients on UFH) or an abnormal prothrombin activity and/or platelet count (two on MF 701, four on UFH) on admission. Of the 316 patients analysed, 254 underwent DVT surveillance by impedance plethysmography alone (MF 701, 129; UFH, 125) and 62 by impedance plethysmography and fibrinogen uptake test (MF 701, 28; UFH, 34).

The four patient subgroups were well matched for age, sex, and known risk factors for DVT (Table 1). A retrospective analysis of risk factors for bleeding showed that 13.3 per cent of the total study sample (MF 701, 10.8 per cent; UFH, 15.7 per cent – an insignificant difference) had liver dysfunction on admission, as defined by abnormality in two or more of four relevant tests (aspartate and alanine aminotransferases,

Table 1 Patient characteristics on admission

	Surveillance method			
	IPG		IPG plus FUT	
	MF 701 (n = 129)	UFH (n = 125)	MF 701 (n = 28)	UFH (n = 34)
Mean (s.d.) age (years)	58(10)	59(10)	58(10)	57(10)
Sex ratio (M:F)	73:56	61:64	10:18	18:16
Risk factors for DVT (%)				
Malignancy	45	34	29	33
Age > 65 years	24	25	29	21
Varicose veins	4	9	14	15
Immobilization > 48 h	8	10	14	6
Obesity	9	8	11	9
Diabetes	6	10	14	6
Previous myocardial infarction	3	4	0	3
Chronic lung disease	2	3	4	6
Other	2	3	4	0

IPG, impedance plethysmography; FUT, ^{125}I -radiolabelled fibrinogen uptake test; MF 701, dermatan sulphate; UFH, unfractionated calcium heparin; DVT, deep vein thrombosis. Differences between the four subgroups were not statistically significant.

alkaline phosphatase, serum bilirubin). The operations performed are described in *Table 2*; most were abdominal. The type and duration of anaesthesia and the duration of prophylaxis were also similar between subgroups (*Table 2*).

Efficacy

Data from DVT surveillance tests were obtained for all but two patients (both allocated to impedance plethysmography and MF 701) who were transferred to the intensive care unit shortly after surgery. Sixteen patients developed a positive surveillance test, six in the impedance plethysmography group and ten in the impedance plethysmography and fibrinogen uptake test group. Because of patient refusal or technical problems, results from venography could be obtained in only six cases (all in the impedance plethysmography plus fibrinogen uptake test group), with positive results in two, both showing a calf vein thrombosis. Of the four venograms that were negative for DVT, two showed alterations of the superficial veins, which might explain the false positivity of the fibrinogen uptake test.

The resulting DVT rate, as determined by the study outcome criteria, is shown in *Table 3*. In the impedance plethysmography group, the DVT rate was 3.1 per cent for patients on MF 701 and 1.6 per cent for those on UFH. In the impedance plethysmography plus fibrinogen uptake test group, the DVT rate was 7.1 per cent on MF 701 and 11.8 per cent on UFH. These differences between treatments were not statistically significant. If the two diagnostic groups are pooled (*Table 3*), the difference in DVT rate between treatments was 0.1 per cent (95 per cent confidence interval -4.1 to 4.3 per cent).

All patients remained free from signs of DVT during their hospital stay. Pulmonary embolism was suspected in two patients allocated to impedance plethysmography and UFH, operated on respectively for lung and pancreatic cancer, who died from respiratory failure before lung scans could be performed; their impedance plethysmographs were negative and autopsy was impossible for legal reasons. A third in-hospital death in the UFH group was due to acute hepatic failure in a patient with liver cirrhosis. There were two in-hospital deaths for patients on MF 701, due respectively to intestinal occlusion after total gastrectomy and to an undetermined cause after palliative surgery for gastric cancer with liver metastases.

Safety

Intraoperative bleeding was judged to be excessive in two patients on MF 701 and in three patients receiving UFH. Details on bleeding after operation are shown in *Table 4*. Both intervention site and extraoperative site haemorrhages were more frequent with UFH; the overall incidence of bleeding was 5.7 per cent with MF 701 and 17.6 per cent with UFH ($P < 0.01$). The prevalence of liver dysfunction in 37 patients who bled was 38 per cent. Reoperation and treatment withdrawal due to bleeding were both significantly more frequent with UFH (*Table 4*). Blood transfusion requirements were similar in the two treatment groups during operation, but significantly greater with UFH after operation (*Table 4*). Bruising at the injection site was noted in one patient on MF 701 and in 39 patients receiving UFH ($P < 0.01$). There

Table 2 Surgical intervention and treatment

	Surveillance method			
	IPG		IPG plus FUT	
	MF 701 (n = 129)	UFH (n = 125)	MF 701 (n = 28)	UFH (n = 34)
Type of surgery (%)				
Upper gastrointestinal tract	9.3	4.8	7.1	2.9
Lower gastrointestinal tract	5.4	8.0	3.6	0.0
Liver	7.0	3.2	3.6	5.9
Biliary tract	27.1	37.6	35.7	38.2
Pancreas	3.1	1.6	7.1	2.9
Hernioplasty	21.7	23.2	25.0	23.5
Lung	9.3	5.6	0.0	8.8
Breast	12.4	8.0	10.7	14.7
Other	4.7	8.0	7.1	2.9
Type of anaesthesia (%)				
General	89.9	86.5	89.3	84.8
Epidural	10.1	13.5	10.7	15.2
Mean(s.d.) duration of anaesthesia (min)	200(95)	179(91)	200(96)	170(91)
Mean(s.d.) duration of treatment (days after operation)	11.9(5.2)	10.8(4.8)	12.0(5.3)	10.4(4.6)

Abbreviations are given in *Table 1*. Differences between the four subgroups were not statistically significant

Table 3 Observed deep vein thrombosis rates

	Surveillance method					
	IPG		IPG plus FUT		Total patient sample	
	MF 701 (n = 127)	UFH (n = 125)	MF 701 (n = 28)	UFH (n = 34)	MF 701 (n = 155)	UFH (n = 159)
Positive IPG or FUT, positive venography	0	0	1	1	1	1
Positive IPG or FUT, venography not performed	4	2	1	3	5	5
Total	4 (3.1)	2 (1.6)	2 (7.1)	4 (11.8)	6 (3.9)	6 (3.8)

Values in parentheses are percentages. Abbreviations are given in *Table 1*. Differences between MF 701 and UFH were not statistically significant

Table 4 Clinically overt bleeding and blood transfusion requirements

	Treatment method		P
	MF 701 (n = 157)	UFH (n = 159)	
Bleeding from operation site*	7	20	0.02
Extraoperative site bleeding†	2	8	0.10
Total no. of patients with bleeding	9	28	<0.01
Reintervention due to bleeding‡	1	10	0.01
Treatment withdrawal due to bleeding	2	11	0.02
Patients with intraoperative transfusions	30	21	>0.10
Mean(s.d.) units/patient	2.0(1.4)	2.1(1.2)	>0.10
Patients with postoperative transfusions	16	29	0.04
Mean(s.d.) units/patient	1.6(1.4)	2.7(2.6)	0.10

Abbreviations are given in Table 1. *Wound haematoma; bleeding from drains; bleeding from surgical anastomoses of the gastrointestinal or biliary tract; other haemorrhages from the operation site. †Spontaneous gastrointestinal haemorrhage; haematuria; injection site haematoma; epistaxis. ‡Including wound haematoma evacuation

Table 5 Haematological parameters of patients having complete data for all time points

	Treatment method	
	MF 701	UFH
Haemoglobin (g/dl)		
n	154	153
Admission	13.2(1.8)	13.3(1.7)
Day 1	12.9(1.8)	12.8(1.8)
Day 3	12.3(1.8)	12.4(2.1)
Day 7	12.0(1.7)	12.1(1.8)
Haematocrit (%)		
n	154	153
Admission	39.6(4.6)	39.8(5.0)
Day 1	38.8(5.2)	38.6(5.1)
Day 3	37.1(5.4)	37.1(6.0)
Day 7	36.1(4.9)	36.6(4.9)
Platelet count (× 10 ⁹ /litre)		
n	123	126
Admission	253(80)	261(77)
Day 1	247(77)	251(97)
Day 7	287(89)	276(100)

Values are mean(s.d.); days 1, 3 and 7 are times after operation. Abbreviations are given in Table 1. Differences between treatment groups were not statistically significant

were no significant differences in mean haemoglobin levels, haematocrit and platelet counts between the treatment groups (Table 5).

There were no adverse clinical events, other than those of haemorrhagic nature, that could be attributed to the drugs under study. Two of the patients who died (one on MF 701, one on UFH) showed a terminal drop in platelet count that was considered to result from blood loss (both patients had had major bleeding with a fall in haemoglobin and haematocrit) and the underlying illness (metastatic cancer and liver cirrhosis, respectively). Routine serum biochemistry tests did not show any significant difference between the treatment groups.

Drug monitoring

The activated partial thromboplastin time was unaffected by either treatment. The mean(s.d.) MF 701 plasma concentration in patients given this drug was 0.37(0.37) µg/ml on day 1 after operation (n = 24) and 0.72(0.61) µg/ml on days 6, 7 or 8 after operation (n = 23).

Follow-up

Follow-up information after 3 months was obtained for 297 (MF 701, 148; UFH, 149) of the 311 survivors. The only thromboembolic event was a non-fatal pulmonary embolism in a UFH-treated patient. Eight MF 701-treated patients and nine UFH-treated patients died in the course of follow-up, apparently from progression of underlying malignancy.

Patients excluded from analysis

None of the patients excluded from analysis (two on MF 701, six on UFH) had evidence of DVT. None of the patients on MF 701 had haemorrhagic complications. Three of the patients on UFH had postoperative bleeding; one of them, who had liver cirrhosis with portal hypertension, required reintervention, had disseminated intravascular coagulation and eventually died.

Discussion

This study provides the first assessment of MF 701 as a prophylactic agent against DVT after general surgery. MF 701 was as effective as the reference treatment with UFH, but significantly safer. This study raises some methodological issues that are worth considering in assessing its results.

In the absence of previous clinical data on DVT prevention, the dose of MF 701 was selected on the basis of its antithrombotic potency relative to UFH, according to the experimental data available at the time¹⁵. Concerning UFH, the standard thrice-daily regimen originally validated by the International Multicentre Trial² was chosen instead of the twice-daily regimen used in several further studies. The two regimens have been shown by a large meta-analysis to be equivalent in both prophylactic efficacy and haemorrhagic effects⁴. Therefore, the UFH dose used was not a relevant factor in the comparison with MF 701.

As MF 701 was administered i.m. rather than s.c. (because of the 2-ml injection volume) and with a different time schedule from that for UFH, making the study blind would have required one or three daily placebo injections in the UFH or MF 701 groups, respectively, which was regarded as unethical. Moreover, minimal injection site effects often caused by UFH might have allowed its distinction from placebo. Although administration of the study drugs was not performed blind, possible sources of bias were controlled by consecutive patient recruitment, blind assessment of the efficacy outcomes, and objectivity of the safety criteria.

The combination of the fibrinogen uptake test and impedance plethysmography is the most sensitive non-invasive way of detecting DVT in patients at risk²⁵. However, radioprotection measures implemented in this hospital limited the frequency of use of the fibrinogen uptake test, thereby preventing its performance in consecutive patients. Serial impedance plethysmography was adopted for all patients, thereby accepting a reduced sensitivity²⁵ but preserving the advantages of consecutive recruitment and adequate sample size. The addition of the fibrinogen uptake test was restricted to a subgroup, which was extracted randomly to prevent selection bias.

The patient sample was at relatively high risk of DVT, as indicated by the prevalence of malignancy (37.8 per cent) and the mean duration of operation. The limited sensitivity of impedance plethysmography alone was confirmed by the DVT rate detected in this diagnostic group (2.4 per cent) compared with that in the impedance plethysmography plus fibrinogen uptake test group (9.7 per cent). Both these figures are of the same order as those from recent studies with UFH and low molecular weight heparins, which range from 2.5 to 8.3 per cent⁸⁻¹¹; most of these studies used a fibrinogen uptake test alone to detect DVT.

Although the absolute incidence of DVT in patients undergoing impedance plethysmography alone was underestimated, this should not have affected the assessment of the

relative antithrombotic activities of MF 701 and UFH. In fact, their equal efficacy, as shown in the impedance plethysmography group, was confirmed by the results of patients undergoing impedance plethysmography and the fibrinogen uptake test. In the total study sample, DVT rates according to treatment were almost identical; the confidence interval indicated that MF 701 could be, at worst, only slightly inferior to UFH, or at best only slightly superior. The lack of clinically important differences in the efficacy of the two drugs was also supported by the data on symptomatic thromboembolism and mortality, both in the hospital and during follow-up.

The incidence of bleeding observed in the UFH group may seem relatively high; however, previous studies on general surgical patients have reported widely varying data on haemorrhage, both in UFH-treated and untreated control groups²⁶, reflecting the use of different criteria to define bleeding. In this study every clinically overt haemorrhage, irrespective of whether it was judged a 'normal' consequence of the operation or an abnormal event, was recorded. Moreover, the patient sample was characterized by a substantial prevalence of liver dysfunction, a condition that was found to be strongly associated with the risk of haemorrhage. The reduced incidence of bleeding with MF 701 compared with UFH was not only statistically significant but also clinically important, as shown by the need for fewer reinterventions and postoperative transfusions in the former group. As a result of the greater amount of blood transfused in the UFH group, no differences were seen in haemoglobin and haematocrit values.

In conclusion, the results of this study indicate that a single daily injection of 100 mg MF 701 is as effective as a standard UFH regimen in preventing DVT after major general surgery. The study further demonstrates that MF 701 is significantly less haemorrhagic than UFH and does not cause other side-effects. To our knowledge, no other form of pharmacological prophylaxis of DVT has so far been proven to be safer than UFH in general surgery. Improving the risk:benefit ratio of DVT prophylaxis remains a major issue in the management of surgical patients and MF 701 appears from present data to have promise. Further studies of dermatan sulphate are worth conducting to confirm the present findings.

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Infected femoral pseudoaneurysm in intravenous drug abusers

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The result of surgical treatment of 21 infected femoral pseudoaneurysms in 19 intravenous drug addicts was evaluated. Eight pseudoaneurysms involved only the common or superficial femoral artery and 13 involved the femoral bifurcation. Excision and ligation was performed as the sole procedure in 19 instances, and revascularization by bypass through the obturator route was carried out in two. The mean follow-up was 12.3 months. One patient required an above-knee amputation. The resultant ischaemia was greater after triple vessel ligation (mean ankle:brachial pressure index (ABPI) 0.41) than single vessel ligation (mean ABPI 0.58). Postoperative bleeding occurred in one patient. Intermittent claudication was present in 14 patients after excision and ligation. Claudication was universal and more severe after triple than after single vessel ligation. There was no subsequent limb loss. Excision and ligation is safe and is the treatment of choice for infected femoral pseudoaneurysm in drug addicts.

Intravenous drug abuse is an increasing problem in Hong Kong. The management of an infected pseudoaneurysm of the femoral artery (Figure 1) is difficult. Treatment of this condition varies from excision and ligation of the involved vessel to ligation and routine revascularization¹. Some have adopted a more selective attitude towards revascularization, either simultaneously with ligation²⁻⁴ or as a delayed procedure⁵.

The method of treatment has been guided by considerations of limb loss and graft sepsis. The results of treating this condition have been reviewed with an evaluation of the need for revascularization immediately or subsequently.

Patients and methods

Between May 1986 and December 1990, 19 patients with 21 infected femoral pseudoaneurysms were treated in this department. The patients were Chinese men with an age range of 31-63 (mean 43) years. The history of intravenous drug abuse ranged from 6 months to 15 years. Eight pseudoaneurysms occurred in the left groin, nine in the right, and two patients had bilateral femoral pseudoaneurysms.

All patients presented with a pulsating groin mass; bleeding was present in 12 patients. Two patients presented with severe pain suggestive of impending rupture and two had septicaemia on admission. Arteriography was performed in seven patients before operation for confirmation of the diagnosis (Figure 2). The pseudoaneurysm ruptured during angiography in one patient and immediate operation was required.

Two patients had undergone iliofemoral bypass before admission to this hospital. Both grafts, placed in the subcutaneous plane through contaminated fields, were infected and had to be taken down. The arteries were ligated. In two other patients the pseudoaneurysm was mistaken for an abscess and incised, leading to brisk bleeding.

Operation was performed on all patients as an emergency. All received systemic antibiotic cover. General anaesthesia was used in 18 patients and spinal anaesthesia in one. A suprainguinal incision was used to control the external iliac artery before making a second incision in the medial thigh distal to the pseudoaneurysm to gain access to the superficial femoral artery. Heparin was not given. Clamps were placed on the two arteries and the pseudoaneurysm was entered. Where the common femoral bifurcation was involved, back-bleeding from the profunda femoris artery would be brisk and this artery often had to be plicated from within the sac. The involved arteries were ligated, the sac excised, and necrotic tissue debrided. Wound cultures were routinely taken.

Simple excision and ligation was performed on 19 limbs without any revascularization procedure. In two patients (one with a common femoral and the other a bifurcation pseudoaneurysm) a simultaneous obturator bypass was performed using expanded polytetrafluoro-

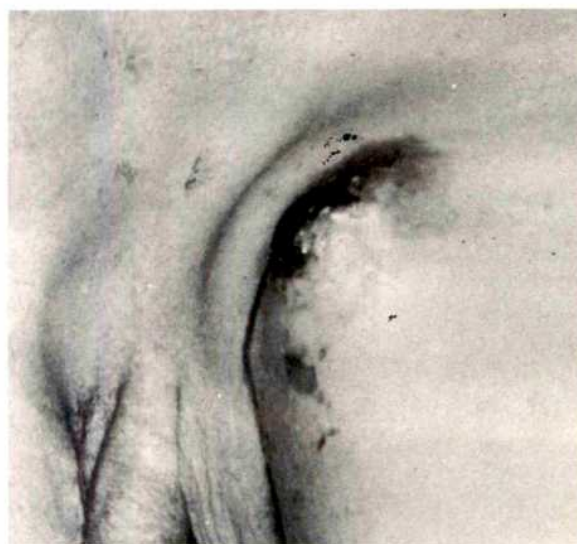


Figure 1 Infected femoral aneurysm in a drug addict

ethylene grafts from the external iliac to the popliteal artery, with ligation of the pseudoaneurysm.

All wounds were left open and the patients were hospitalized until the wounds had healed by granulation. The foot circulation was monitored clinically and documented objectively using the Doppler technique. Ankle:brachial pressure indices (ABPIs) were measured for all patients from the first day after operation. Preoperative measurements were made in eight limbs.

Patients were followed for periods ranging from 2 to 36 (mean 12.3) months. The viability of the limbs and the degree of claudication were noted. Serial ABPIs were measured in all patients during follow-up visits to the vascular clinic.

Results

Patients were divided into two groups based on the location of the pseudoaneurysm and the vessels involved. Group 1 consisted of eight pseudoaneurysms which involved only a single vessel, either the common femoral artery (five) or the superficial femoral artery (three). Group 2 comprised 13 limbs in which the bifurcation of the common femoral artery was affected and all three femoral vessels were involved. In group

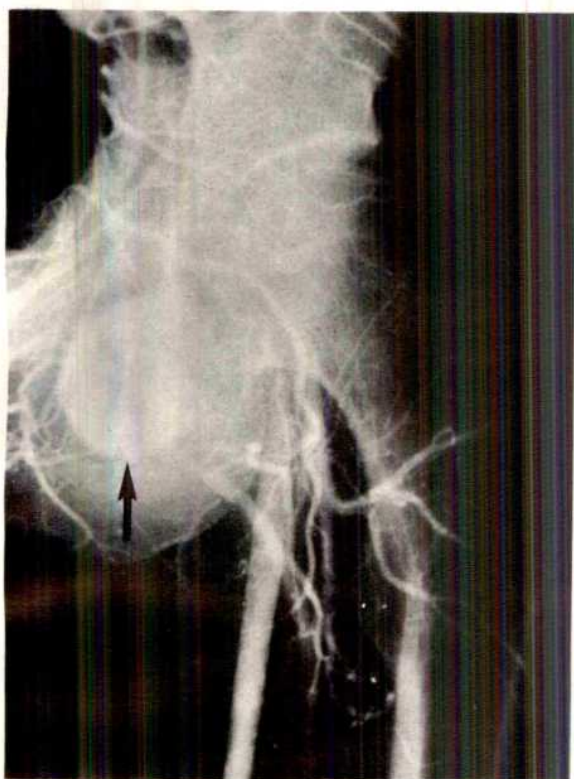


Figure 2 Arteriogram showing leakage of contrast (arrow) into a pseudoaneurysm of the left common femoral artery

1 only the diseased artery was ligated (single vessel ligation) but in group 2 ligation of the common, superficial and deep femoral arteries was performed.

Since all operations were carried out on an emergency basis, preoperative ABPIs were measured in only eight limbs (three from group 1, five from group 2). Indices ranged from 0.93 to 1.07 with a mean of 0.99.

Group 1 (n = 8)

One common femoral artery pseudoaneurysm was repaired primarily but the patient developed a secondary haemorrhage at 1 week and required ligation with an obturator bypass. The graft became blocked 5 months later and the patient had severe claudication. In the other seven patients ligation of the artery was performed without revascularization. The immediate postoperative ABPIs in this group ranged from 0.36 to 0.73 (mean 0.58).

Four of the seven patients with single vessel ligation remained asymptomatic on follow-up but three had mild claudication not affecting daily activities. None of the limbs showed signs of critical ischaemia and no further revascularization procedures were performed.

Group 2 (n = 13)

There was one complication in this group: bleeding from a dehiscence common femoral stump 3 weeks after ligation. This was resutured. In 12 of the 13 limbs no revascularization was attempted. The postoperative ABPIs ranged from 0.13 to 0.59 (mean 0.41). In the remaining patient an obturator bypass was carried out, the index stabilized at 0.8, and the patient was asymptomatic.

In one patient (who had had a similar pseudoaneurysm on the other leg 3 years earlier), critical ischaemia developed immediately after triple ligation. Reconstruction was not possible because of coincidental sepsis in the popliteal fossa; the leg became gangrenous, and an above-knee amputation was required.

The other 11 patients subsequently developed claudication on follow-up; in four this was severe enough to be disabling.

No critical ischaemic changes were noted. No further revascularization was carried out because the patients refused treatment or it was not considered worthwhile. None of these patients had lost a limb.

On long-term follow-up the ABPIs for most patients improved slightly to the 0.6–0.7 range and remained stable thereafter.

Wound swabs were taken from 14 patients. *Staphylococcus aureus* was reported in 11 instances and *Pseudomonas aeruginosa* in two.

Discussion

The correct management of infected femoral pseudoaneurysm in drug addicts is uncertain. Ligation and excision of the involved vessel⁴ is associated with a high amputation rate (14–21 per cent)^{3,5}. Some have therefore proposed a policy of selective revascularization, simultaneous with the ligation^{2–4} or delayed until critical ischaemia develops⁵. Routine simultaneous revascularization with good limb salvage and low complication rates has been reported¹.

Simultaneous vascular reconstruction in these patients is difficult because the procedure is complicated and prolonged, and undiseased autologous veins are scarce in drug addicts. A synthetic graft is often required and has to be placed in a potentially infected field. The rate of graft sepsis and blockage is high (7–83 per cent)⁶ and the results disastrous. Despite immediate revascularization, amputation rates may still be as high as 33 per cent⁵, no different from the results of ligation alone. There is no reliable method to predict which patients require revascularization.

Excision and ligation alone in 19 limbs was associated with the loss of one limb. This policy appears safe as rebleeding occurred in one instance from a dehiscence artery stump. Such a simple procedure appears to be as effective in limb salvage as revascularization. Distal circulation is maintained via collaterals in the buttock and thigh to supply the popliteal artery. The only patient undergoing amputation had thrombosis of the superficial femoral and popliteal arteries and the femoral vein from more than 10 years of injection. Limb loss was anticipated but a bypass operation was precluded by sepsis in the thigh and popliteal fossa.

The nature of this condition and the patient population compromise complete follow-up, and the outcome of the treatment policy is not always known. The mean duration of follow-up in this series was more than 12 months but an ABPI of 0.4–0.5 immediately after simple excision and ligation was satisfactory and suggests that the procedure is safe.

Many patients developed intermittent claudication after excision and ligation. The degree of ischaemia should be more severe after triple than single vessel ligation. This was confirmed by the severity of claudication and postoperative ABPIs. All patients developed claudication after triple ligation and in many this was severe. Delayed revascularization was not considered relevant because of poor patient compliance and the risk that the graft could be used for vascular access with increased risk of infection. No late amputation was required.

Clinical differentiation of a pseudoaneurysm from a groin abscess is sometimes difficult and erroneous diagnosis and attempted drainage in two patients led to brisk bleeding. Conventional and digital subtraction arteriography is said to be essential for diagnosis³. In this series diagnosis was based on a history of intravenous drug abuse and a pulsating groin mass, although bleeding from the mass in 12 patients made the diagnosis certain. As routine ligation without revascularization usually gives a good result, the anatomical information obtained from an arteriogram is not necessary. Arteriography is not without risks, as one pseudoaneurysm ruptured during the examination. Furthermore, coexisting distal vessel disease is uncommon in this group of young patients.

Excision and ligation is a simple and safe method with a low risk of early limb loss. It is recommended as the primary

treatment of infected femoral pseudoaneurysm in intravenous drug addicts. Residual claudication is common but not severe and subsequent limb loss is minimal.

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Tying a laparoscopic knot

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Since the introduction of laparoscopic cholecystectomy in 1987, several intra-abdominal surgical procedures have been attempted laparoscopically. Difficulty in tying knots resulted in the development of clip applicators and 'endoloops' – preformed loops of catgut ligatures for securing vessels and other intra-abdominal structures. While these methods are effective, clip applicators are expensive and there is potential for the 'hangman's knot' to slip. Tying knots using instruments within the abdominal cavity is difficult and therefore a simple method of knot tying, which can be used in laparoscopic procedures, has been developed.

Method

A monofilament suture or ligature is introduced into the abdominal cavity using a needle holder or grasping forceps via a 5-mm cannula until one end of the suture protrudes through the cannula (Figure 1). The intra-abdominal end of the suture is placed around the structure to be ligated. The ends of the suture are brought out through the cannula until both ends are outside the abdomen. A single or double

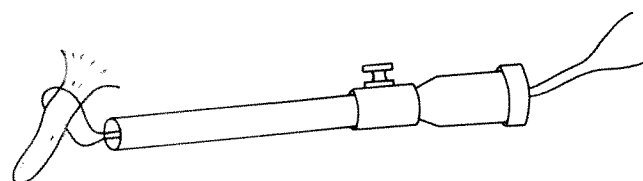


Figure 1 A suture is placed around an intra-abdominal structure and both ends are brought out through a cannula

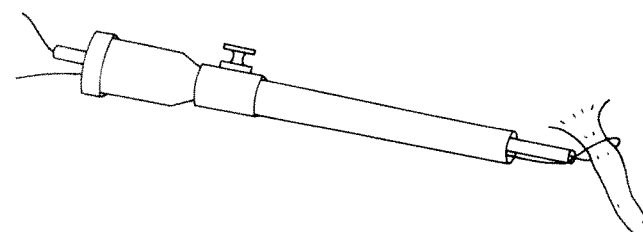


Figure 2 The pushing tube, which has been placed over one end of the suture, advances the externally formed knot into the abdominal cavity

classical surgical knot is made and a pushing tube slid over one of the two threads. Holding the ends of both threads, the knot is pushed into the abdominal cavity and snugged down to the desired tension (Figure 2). A second knot is made in the same manner and pushed down on to the first knot. Redundant suture is cut with scissors and removed through the cannula.

This is a simple and reliable method of tying knots during laparoscopic surgery. The application of this technique may broaden the scope of laparoscopic procedures.

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Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery

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The frequency of infection in 197 patients undergoing elective colorectal surgery and having either no blood transfusion, transfusion with whole blood, or filtered blood free from leucocytes and platelets was investigated in a prospective randomized trial. Natural killer cell function was measured before operation and 3, 7 and 30 days after surgery in 60 consecutive patients. Of the patients 104 required blood transfusion; 48 received filtered blood and 56 underwent whole blood transfusion. Postoperative infections developed in 13 patients transfused with whole blood (23 per cent, 95 per cent confidence interval 13–32 per cent), in one patient transfused with blood free from leucocytes and platelets (2 per cent, 95 per cent confidence interval 0.05–11 per cent) and in two non-transfused patients (2 per cent, 95 per cent confidence interval 0.3–8 per cent) ($P < 0.01$). Natural killer cell function was significantly ($P < 0.001$) impaired up to 30 days after surgery in patients transfused with whole blood. These data provide a strong case against the use of whole blood transfusion in patients undergoing elective colorectal surgery.

Blood transfusion is associated with certain risks and during the past three or four decades attention has been drawn to its possible effects on the immune system. Blood transfusion produces immunosuppression and this may have beneficial clinical consequences, e.g. in renal transplantation, where transfusion-induced changes are associated with a decreased rate of allograft rejection^{1–3}. Significant decreases in the rate of recurrence of Crohn's disease have also been described after transfusion⁴.

In other conditions the immunosuppressive action of blood transfusion may be deleterious. Perioperative transfusion increases the recurrence rate and decreases survival rates in patients with colorectal^{5,6} and breast⁷ cancer. These studies have been retrospective and it has not been proven that blood transfusion is the direct cause of these effects.

Blood transfusion may be a significant factor affecting postoperative immune system function, leading to an increased susceptibility to infection^{8,9} and multiple organ failure¹⁰.

Leucocytes may mediate the effects of cancer recurrence and allograft rejection¹¹; whole blood has a better effect than packed red cells on allograft survival¹². The underlying mechanism for this is not clear but it has been demonstrated that whole blood transfusion causes reduced natural killer (NK) cell function and a decreased T helper:T suppressor lymphocyte ratio¹³. Whole blood amplifies the impairment in delayed hypersensitivity after operation¹⁴. Blood free from white cells may be the safest preparation for preventing postoperative infection when transfusion is necessary.

A prospective study was designed to compare the frequency of infection in patients undergoing elective colorectal surgery and either having no transfusion, or being randomized to transfusion with whole blood or blood free from white cells. Immune function was monitored in all patients from one of the three participating departments of surgery.

Patients and methods

All patients admitted for elective colorectal surgery between August 1989 and September 1990 were considered for inclusion in the study,

which had been approved by the local ethical committee. The exclusion criteria were: age less than 18 years; acute colorectal surgery; and immunosuppressive treatment. After giving informed consent, patients in whom transfusion was indicated were randomly allocated using sealed envelopes to receive either whole blood or blood free from white cells. The latter was obtained by passing whole blood through a filtering device (Pall-filter; MEDA, Copenhagen, Denmark) thereby reducing the leucocyte and platelet content by 99.98 per cent. Red cells and plasma passed through the filter, which was mounted at the bedside and placed between the blood bag and the transfusion tube. All blood used was less than 3 weeks old. The indications for transfusion were a haematocrit before operation of less than 0.35 or a haemoglobin level below 7.2 mmol l⁻¹. Intraoperative or postoperative transfusions were given according to the haemodynamic status of the patient.

All patients received cefuroxime 3 g and metronidazole 1.5 g intravenously as one preoperative dose of antibiotic prophylaxis. Oral antibiotics were not given. The bowel was prepared with oral laxative and saline enema or Golytely (AAKH, Aarhus, Denmark).

After surgery, abdominal wounds were closed with absorbable sutures for the peritoneum and fascia and non-absorbable sutures to the skin. Antibiotics were not used in the wounds; neither were subcutaneous drains.

Follow-up examination included daily wound inspection by an independent assessor from the third day after operation until suture removal or patient discharge. All patients were followed in the outpatient clinic for 30 days after operation. Abdominal wound infection was defined as accumulation of pus with spontaneous discharge or requiring surgical drainage. Wounds with purulent discharge after the patient returned home were included in the infected group. Deep surgical infection consisted of: (1) intra-abdominal abscess defined as an intraperitoneal or pelvic collection of pus diagnosed by ultrasonography, laparotomy or spontaneous discharge; and (2) septicæmia defined as the presence of spiking fever associated with positive blood culture. The frequency of anastomotic leakage was diagnosed by fever and faecal fistula or peritonitis. Pneumonia was diagnosed by fever and infiltrate on chest radiography. Other surgical complications such as abdominal wound dehiscence, bleeding and ileus were considered separately.

Blood samples for measurement of haematocrit, haemoglobin, serum albumin, immunoglobulin A (IgA), IgG, IgM and NK cell function were taken before operation and on days 3, 7 and 30 after operation. Cytomegalovirus (CMV) titre (IgG and IgM), Epstein-Barr

virus (EBV) titre (IgG and IgM) and herpes virus titre were measured before operation and 30 days afterwards.

NK cell function was evaluated in 60 consecutive patients from one of the participating departments of surgery by a modified whole blood assay as previously described¹⁵. A volume of 100 µl heparinized blood was added to varying numbers of ⁵¹Cr-radiolabelled K562 target cells. After a 4-h incubation at 37°C supernatants were counted for isotope release and cytotoxicity expressed as the percentage specific ⁵¹Cr release according to the formula:

$$\text{Percentage } ^{51}\text{Cr release} = \frac{(E - b) \times \left(\frac{V_t - V_b \times H}{V_t} \right) - (S - b)}{(M \times 0.8) - S} \times 100$$

where V_t is the total assay volume, V_b is the volume of blood assayed, H is the percentage haematocrit/100, E is the total test count, b is the background c.p.m., S the spontaneous and M the maximal ⁵¹Cr release. For each patient sample assayed, blood from a normal control person with known cell activity was tested in parallel as a control. Patients in whom the protocol was violated during operation were withdrawn from evaluation.

Differences between groups and variables of patients with and without infection were tested using the χ^2 test or Student's t test. Results were considered significant at $P < 0.05$ and 95 per cent confidence intervals for differences were calculated.

Results

A total of 215 patients entered the study, of whom 18 were withdrawn. Protocol violation occurred in 15 patients because no resection or extirpation was deemed necessary. Three patients withdrew from the study after randomization. The remaining 197 patients were suitable for evaluation of whom 104 (52.8 per cent) required blood transfusion. Of these patients 43 (46.2 per cent) received leucocyte-free blood and 56 (53.8 per cent) whole blood transfusion. Preoperative characteristics of the patient groups are shown in Table 1. There were more patients with benign polyps and the haematocrit on admission was higher in the non-transfused group. There were more sigmoid resections and closure of colostomies in the non-transfused group (Table 2) with more patients undergoing proctocolectomy and abdominoperineal resection in the transfused group. There were no differences in operative procedures between patients transfused with filtered blood or whole blood (Table 2). More transfused patients underwent drainage of the abdominal cavity (Table 3). There were no differences in bowel preparation.

The 60 patients with measurement of NK cell function were comparable to the other patients with respect to clinical and surgical details. The diagnoses in this group were: malignancy

Table 2 Surgical characteristics of the patient groups

	Non-transfused	Transfused	
		Filtered blood	Whole blood
Ileocolostomy	0	0	1
Right hemicolectomy	15	13	10
Left hemicolectomy	3	2	5
Sigmoid resection	31*	7	6
Anterior resection	9	5	5
Low anterior resection	5	6	3
Other resection	5	0	4
Colostomy	3	1	2
Hartmann's operation	2	2	2
Colorectal anastomosis	7	1	3
Closure of colostomy	8*	0	0
Colectomy and ileostomy	1	0	1
Proctocolectomy	0*	2	3
Abdominoperineal excision	4*	9	11

Filtered blood, blood free from leucocytes and platelets. * $P < 0.05$ (non-transfused versus transfused patients, χ^2 test)

Table 3 Perioperative characteristics of the patient groups

	Non-transfused	Transfused	
		Filtered blood	Whole blood
Median (range) duration of surgery (min)	137 (60–300)	172 (55–320)	158 (50–320)
Drainage of abdominal cavity	31*	35	35
Assessment of bowel content			
Clean bowel	80	44	43
Faecal loaded bowel	8	2	8
Faecal contamination of abdominal cavity	5	2	5

Filtered blood, blood free from leucocytes and platelets. * $P < 0.05$ (non-transfused versus transfused patients, χ^2 test)

Table 4 Septic complications

	Non-transfused	Transfused	
		Filtered blood	Whole blood
Abdominal wound sepsis	2	1	13*
Intra-abdominal abscess	0	0	3
Septicaemia	0	0	1

Filtered blood, blood free from leucocytes and platelets. * $P < 0.01$ (patients transfused with whole blood versus patients transfused with filtered blood and patients transfused with whole blood versus non-transfused patients, χ^2 test)

Table 1 Clinical details of the patient groups

	Transfused		
	Non-transfused ($n = 93$)	Filtered blood ($n = 48$)	Whole blood ($n = 56$)
Median (range) age (years)	61 (22–81)	68 (35–95)	67 (26–93)
Sex ratio (M:F)	50:43	18:30	19:37
Median (range) weight (kg)	68 (37–116)	66 (39–102)	63 (30–96)
Diabetic	3	3	2
Haematocrit on admission	0.41*	0.36	0.36
Diagnosis			
Malignancy	70	39	43
Benign polyps	4*	0	0
Diverticular disease	7	4	4
Inflammatory bowel disease	5	3	6
Miscellaneous	7	2	3

Filtered blood, blood free from leucocytes and platelets. * $P < 0.05$ (non-transfused versus transfused patients, Student's t test and χ^2 test)

in 48 patients, diverticular disease in five, inflammatory bowel disease in four, benign polyps in one and miscellaneous in two.

Infections developed in 16 patients (8.1 per cent) (Table 4). Three patients developed two or more complications. Thirteen patients transfused with whole blood (23 per cent, 95 per cent confidence interval 13–32 per cent) developed wound sepsis whereas only one patient transfused with filtered blood (2 per cent, 95 per cent confidence interval 0.05–11 per cent) and two non-transfused patients (2 per cent, 95 per cent confidence interval 0.3–8 per cent) developed wound sepsis ($P < 0.01$). Abdominal wound sepsis was diagnosed at a median of 9 (range 4–28) days after surgery. Faecal loading did not correlate with more infections as only two patients had a loaded bowel. Anastomotic leakage occurred in two patients,

Table 5 Blood transfusion and infection

	Filtered blood (n = 48)		Whole blood (n = 56)		P*
	Uninfected	Infected	Uninfected	Infected	
Preoperative transfusion					
No. of patients	18	0	21	2	n.s.
Median (range) units of blood	1 (1-3)	—	2 (1-5)	2.5 (2-3)	
Intraoperative transfusion					
No. of patients	22	1	16	8	<0.05
Median (range) units of blood	2 (1-5)	2	2 (1-3)	2 (1-3)	
Postoperative transfusion					
No. of patients	24	0	18	11	<0.01
Median (range) units of blood	2 (1-4)	—	2 (1-5)	2 (1-3)	

Filtered blood, blood free from leucocytes and platelets. * χ^2 test; n.s., not significant

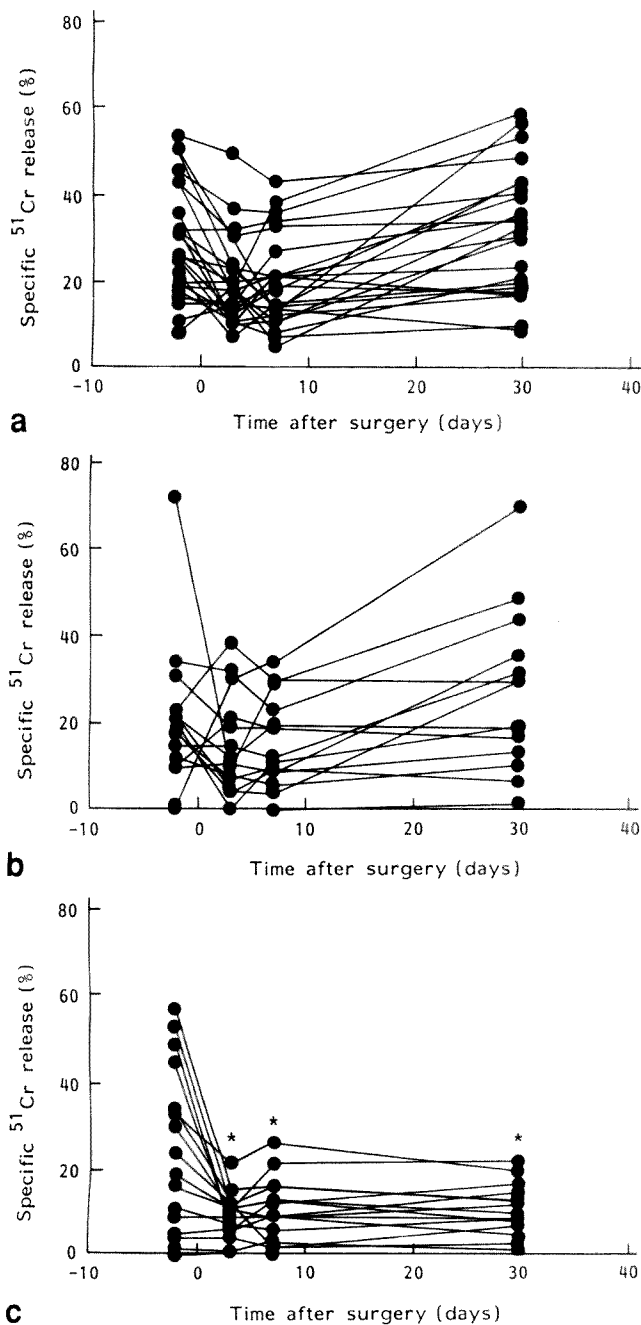


Figure 1 Natural killer cell function in **a** 26 patients receiving no blood transfusion, **b** 15 patients receiving transfusion with blood free from leucocytes and platelets, and **c** 19 patients receiving whole blood transfusion. Values are medians of three assays; the range at each time was always less than 10 per cent of the median value. * $P < 0.001$ (whole blood versus both other groups, Student's *t* test)

one receiving whole blood and one transfused with filtered blood.

Pneumonia developed in eight patients (4.1 per cent): four non-transfused, two transfused with whole blood and two with filtered blood. Surgical complications not related to infection occurred in six patients (3.0 per cent). In four patients a dehiscence of the abdominal fascia was resutured, one patient was operated on because of ileus and one underwent further surgery because of a pulmonary embolism. Only one patient died, resulting in an operative mortality rate of 0.5 per cent. This death occurred in a 93-year-old woman 15 days after surgery and was due to cardiopulmonary insufficiency.

The administration of blood transfusion was similar in the two transfused groups (Table 5). Twenty patients transfused with whole blood and 17 transfused with filtered blood had transfusions both before, during and/or after operation. Only when whole blood was given during or after operation was it significantly associated with the development of infection. In no case was an immediate transfusion reaction resulting in interruption of the transfusion of blood observed.

At day 0 NK cell activity was equal in all three groups. During the first week after surgery a transient and non-significant fall was observed in the non-transfused group as well as in the filtered group (Figure 1). In contrast the group transfused with whole blood exhibited a considerable decrease in NK cell activity during the first week after surgery ($P < 0.001$), and after 1 month these patients still exhibited severe NK cell suppression ($P < 0.001$) (Figure 1).

There were no differences in IgA, IgG and IgM levels between the different groups at any time. Of all the patients 80 per cent had a positive preoperative CMV titre (IgG) and no increase was observed at day 30. All patients had positive EBV and herpes virus titres before operation and no significant increase was observed afterwards. There were no differences in serum albumin levels between the treatment groups at any time in the study period.

Discussion

This study shows that whole blood transfusion during or after operation in patients undergoing elective colorectal surgery was followed by infection in 23 per cent of cases. Those receiving transfused blood free from leucocytes and platelets showed a frequency of infection of only 2 per cent. Transfusion with whole blood was followed by a sustained suppression of NK cell function for 30 days.

In a previous study⁹, 28 per cent of transfused patients developed infection but these patients were not randomized to receive different blood products and the median number of transfusions was more than double that of the present study. Fewer blood transfusions were used in this study because of restrictive indications for transfusion derived from our previous results⁹. This may explain the differences in surgical characteristics of the transfused and non-transfused groups. Blood was given only in the more severe cases and only when

indicated. This may not have been the case in the previous study⁹ where no differences in operative procedures and in blood loss between transfused and non-transfused patients were recorded.

Randomization in the present study separated the possible effects of underlying medical conditions and operative procedures on infection as the groups were well matched with regard to clinical and operative details.

The transient and non-significant fall in NK cell function during the first week in the non-transfused group and the group transfused with filtered blood were similar and probably due to anaesthesia and surgical trauma^{16,17}. The additional effect of whole blood transfusion on postoperative immunosuppression has previously been described^{13,18}. The relationships between transfusion with different blood products, the degree of immunosuppression and the frequency of postoperative infection have not previously been established.

NK cells kill Gram-positive and Gram-negative bacteria by direct contact and secretion of a lytic substance¹⁹. NK cell preparations from different donors show substantial variability in their antibacterial activity and an NK-inhibitory activity of blood transfusion might result in different degrees of vulnerability to postoperative infection.

As those transfused with blood free from leucocytes showed an insignificant decrease in NK cell activity and few infections the leucocytes were probably mediating some of the immunosuppressive effects of whole blood transfusion. Platelets may also depress NK cell activity²⁰. All blood transfusions used were less than 3 weeks old and platelets and platelet products may be responsible for some of the immunosuppressive effect.

In other studies^{5,21} plasma has been implicated as a risk factor in transfusion-associated cancer recurrence. This study shows that plasma does not seem to be a risk factor in transfusion-associated postoperative infection. Although red cells and their components are immunosuppressive *in vitro*²², they were not seen to be so in this study as erythrocytes passed through the filter, such that whole and filtered blood both contained them.

The detrimental effects of blood transfusion may be dose related^{5,13}; in massively transfused patients failure of defence against infections was one of the causes of death¹⁸. This study shows that transfusion with fewer than 5 units of whole blood was associated with an increased frequency of infection.

The immunosuppressive mechanism of leucocytes has not been determined. Removing leucocytes from whole blood preparation removes any microbes eventually phagocytosed by the leucocytes. Transfusion-transmitted infections with viruses such as CMV, EBV or herpes may impair immune function. There was no increase in titre in patients receiving whole blood or having infections.

Different effects of exposure of NK cells to alloantigens have been reported, but prolonged depression of NK cell function has been observed in experimentally induced graft *versus* host disease²³.

The data linking reduced NK cell function to wound infection and blood transfusion are indirect and the development of infection after large bowel surgery is probably multifactorial. Decreased NK cell function may be one of several prerequisites for infection, NK cells being essential to combat bacterial infections¹⁹. Multivariate analyses of larger clinical studies may resolve this issue.

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Effect of aprotinin on neutrophil function after major vascular surgery

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High-dose aprotinin reduces blood loss and blood transfusion requirements during liver transplantation and cardiac and vascular surgery. The mechanism of the haemostatic effect of aprotinin is unclear. A general effect on the anti-inflammatory response may be involved. Because leucocyte activation is part of this process, white cell function was measured in patients undergoing aortic surgery who received high-dose aprotinin therapy ($n = 10$) and was compared with the results from controls who did not ($n = 10$). The test group received an intravenous bolus (2×10^6 kallikrein inhibitor units) of aprotinin after induction of anaesthesia followed by continuous infusion (0.5×10^6 kallikrein inhibitor units/h) until the end of the operation. Blood samples were obtained before operation, immediately after surgery, and 1 and 7 days after operation. Aprotinin maintained significantly better postoperative white cell function as measured by bipolar shape formation ($P < 0.001$), unstimulated nitroblue tetrazolium (NBT) reduction ($P < 0.001$) and chemotaxis ($P < 0.001$). Endotoxin-stimulated NBT reduction was similar in both groups, indicating that neutrophils from treated individuals retained the capacity to respond to oxidative stimuli. Aortic surgery activates neutrophils in vivo, as reflected by impaired chemotaxis and increased superoxide production. Aprotinin protects the cells against this potentially deleterious effect without affecting their ability to respond when provoked. Whether this affects leucocyte interaction with coagulation pathways and contributes to the reduction in blood loss remains to be determined.

Aprotinin is a low molecular weight, broad-spectrum protease inhibitor which has been used for the treatment of acute pancreatitis and conditions associated with hyperplasmin-aemia¹. More recently, high-dose aprotinin has been shown to reduce operative bleeding in cardiovascular^{2,3}, liver transplantation^{4,5} and vascular⁶ surgery and may be effective in other bleeding disorders, including thrombocytopenia⁷. Earlier studies on antiproteases suggested that they may be of value in haemorrhagic shock and that patients suffering from polytraumatic shock may benefit from aprotinin treatment^{8,9}. The action of aprotinin under these circumstances is difficult to ascribe to any specific antiprotease mechanism. Plasmin inhibition, kallikrein inhibition and preservation of platelet number and function, possibly by protecting against plasmin-mediated degradation of platelet membrane adhesive glycoproteins, may be important¹⁰⁻¹⁵. The drug may have effects on peripheral blood leucocytes¹⁶, which are probably involved in the mediation of some shock-related syndromes such as the adult respiratory distress syndrome. The initial aim of using high-dose aprotinin in cardiac surgery was to ameliorate the damaging effects of cardiopulmonary bypass on the lung¹³. Previous studies have reported that neutrophil function may be impaired after surgery, but there are no reports of the effect of aprotinin in this regard. This study, therefore, measured neutrophil function in patients undergoing major vascular surgery under cover of high-dose aprotinin and compared the results with those from controls not given aprotinin.

Patients and methods

Patients

Twenty patients were included in the study. Ten consecutive patients undergoing aortic reconstruction for occlusive disease received aprotinin and were compared with ten controls undergoing various major reconstructive surgical procedures (Table 1). All patients had widespread atherosclerosis confirmed by non-invasive investigations including duplex ultrasonography.

Ethical approval was granted for the trial and all patients gave written consent. The aprotinin group were initially given a test dose of 50000 kallikrein inhibitor (KI) units (Trasylol; Bayer UK, Newbury, UK) slowly over 5 min. This was followed by a bolus dose of 2×10^6 KI units at the beginning of surgery and continuous intravenous infusion of 0.5×10^6 KI units/h until the operation was completed. Both groups were otherwise treated in an identical fashion. Heparinization was reversed by protamine sulphate at the completion of the arterial reconstruction. There were no major differences in the methods of anaesthesia between the two groups and all patients received antibiotic prophylaxis with ampicillin and flucloxacillin.

Neutrophil function assays

Venous blood was collected into heparin (10 units/ml) before operation after induction of anaesthesia, immediately after surgery, and 24 h and 1 week after operation. Total white blood cell count and differentials were performed at each time and three tests of neutrophil function undertaken within 2 h of sampling. The study was not randomized, but laboratory staff were unaware whether samples were from treated or control patients.

Bipolar shape formation assay. A volume of 0.1 ml *N*-formyl-methionyleucylphenylalanine (FMLP, 10^{-8} mol/l; Sigma, Poole, UK) was added to 0.9 ml heparinized whole blood, gently mixed and incubated at 37°C for 20 min. After brief remixing, two blood films

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Table 1 Patient details

Patient no.	Age (years)	Sex	Weight (kg)
Aprotinin group: aortobifemoral bypass			
1	74	F	51
2	72	F	74
3	62	F	63
4	62	F	80
5	60	M	73
6	65	F	69
7	62	M	70
8	66	M	63
9	81	M	75
10	70	M	84
Median	65.5 (62–73)		71.5 (63–77)
Controls			
Aortobifemoral bypass			
1	80	M	76
2	59	F	76
3	67	F	44
4	69	F	71
Carotid endarterectomy			
5	69	M	72
6	65	M	80
7	58	M	62
Aortic aneurysm repair			
8	64	M	71
9	70	M	88
Femorodistal bypass			
10	66	F	68
Median	66.5 (62–69)		71.5 (66–77)

Values in parentheses are 95 per cent confidence intervals

were made, fixed, stained with May–Grünwald–Giemsa stain and examined microscopically. Fifty neutrophils from each film were classified according to shape, as previously described¹⁷. The percentage of bipolar neutrophils was recorded as the mean of the two films. The coefficient of variation (c.v.) for this technique was 9.6 per cent.

Chemotaxis. Chemotaxis was assessed using a modified raft method¹⁸. Leucocyte suspensions containing more than 90 per cent neutrophils were carefully prepared by dextran sedimentation, avoiding procedures likely to activate polymorphonuclear leucocytes¹⁹. The cells were suspended in Hank's balanced salt solution (HBSS), pH 7.4, at a concentration of 5×10^9 /litre. Preparations were judged to be greater than 95 per cent viable by trypan blue exclusion²⁰. Vessels containing the leucocyte suspensions were placed on top of 3.0- μ m pore filters (Millipore, Harrow, UK), which in turn were placed on absorbent discs soaked in chemoattractant (10^{-9} mol/l FMLP or 20 per cent pooled human AB serum). To assess non-directed migration, HBSS was used in place of a specific chemoattractant. In this system, the cells migrate towards the chemotaxin through the pores of the filters, which are subsequently fixed and stained. Chemotaxis was expressed as the leading front (the furthest distance two cells have migrated through the membrane). The c.v. for this technique¹⁷ is 9.2 per cent.

Nitroblue tetrazolium reduction assay. A fresh saturated solution of nitroblue tetrazolium salt (NBT, Sigma) was prepared in 1 ml phosphate-buffered saline (PBS), pH 6.8. A volume of 0.1 ml non-viable bacterial extract (Sigma, stimulated NBT test) or 0.1 ml PBS (non-stimulated NBT test) was incubated with 0.5 ml heparinized whole blood at 37°C for 20 min. NBT solution (0.1 ml) was then added to an equal volume of each preparation and incubated at 37°C for a further 20 min. Cytospin slides were made and stained, without fixing, with methylene green. The percentage of positive (formazan-containing) cells was recorded. The c.v. for this technique is 8.7 per cent.

Statistical analysis

Statistical analysis was performed using the STATGRAPHICS statistical software package (STSC, Rockville, Maryland, USA). Differences between medians were assessed by Mann–Whitney U test. The calculation of 95 per cent confidence intervals used MINITAB (CleCom, Edgbaston, UK).

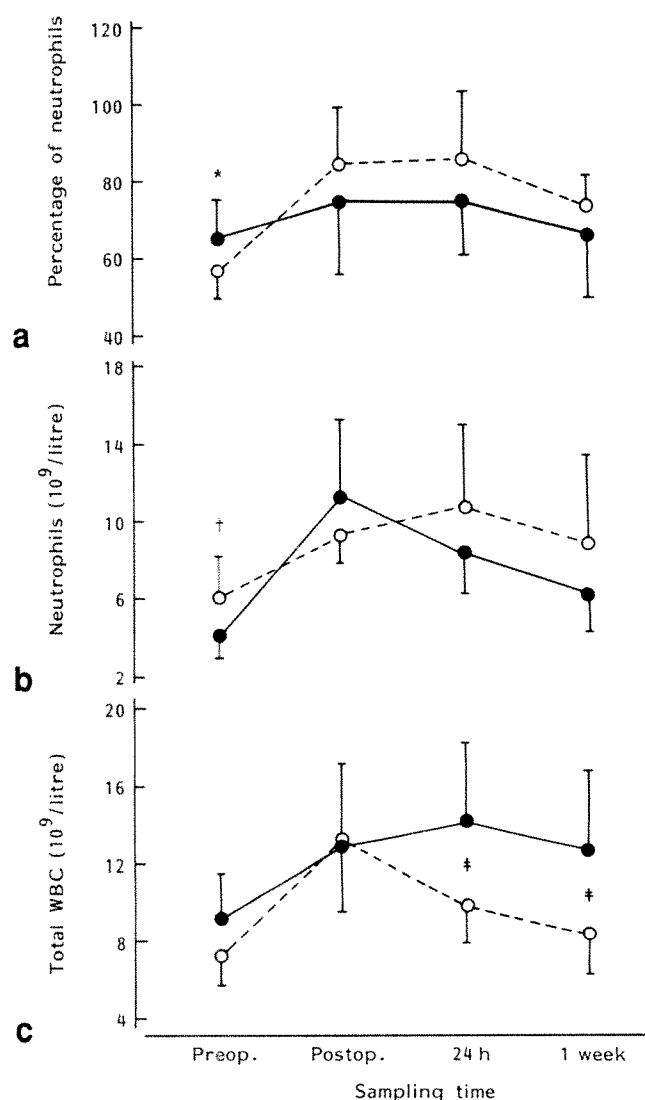


Figure 1 Changes in **a** percentage neutrophils, **b** total neutrophil count and **c** total white blood cell (WBC) count in patients undergoing major vascular surgery with (●) or without (○) aprotinin. Values are median (95 per cent confidence interval). *P < 0.01; †P < 0.02; ‡P < 0.005 (Mann–Whitney U test)

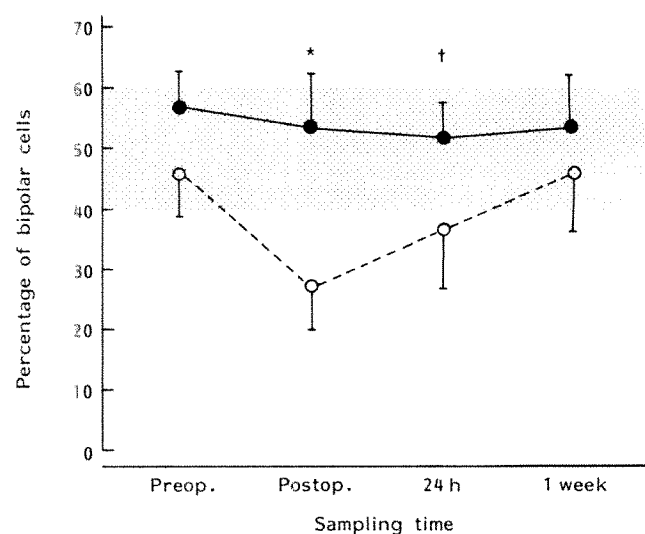


Figure 2 Changes in bipolar shape formation in patients undergoing major vascular surgery with (●) or without (○) aprotinin. Values are median (95 per cent confidence interval); the normal range is indicated by the shaded area. *P < 0.001; †P < 0.002 (Mann–Whitney U test)

Results

All patients completed the study. One individual in the aprotinin treatment group required a femoral embolectomy to retrieve a dislodged atheromatous plaque. Apart from this, there were no perioperative complications in either group, and grafts were functioning satisfactorily on follow-up at 3 months. Blood loss in the aprotinin-treated patients was significantly reduced as previously reported elsewhere⁶.

White blood cell counts (Figure 1) rose immediately after surgery in both groups, although levels in aprotinin-treated patients remained significantly higher than in controls ($P < 0.005$) at 24 h and 7 days after operation (Figure 1c). There was little difference in the total number of neutrophils, although the aprotinin group had significantly higher total ($P < 0.02$) and percentage ($P < 0.01$) neutrophil counts at the start of the study (Figure 1b and a respectively).

The effect of surgery on bipolar shape formation (BSF) is shown in Figure 2. Compared with the aprotinin group, BSF

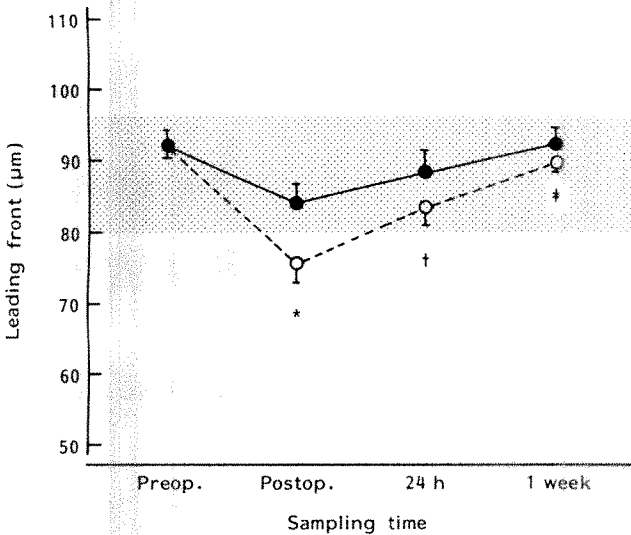


Figure 3 Changes in neutrophil migration towards N-formylmethionyl-leucylphenylalanine (10^{-9} mol/l) in patients undergoing major vascular surgery with (●) or without (○) aprotinin. Values are median (95 per cent confidence interval); the normal range is indicated by the shaded area. * $P < 0.001$; † $P < 0.002$; ‡ $P < 0.05$ (Mann-Whitney U test)

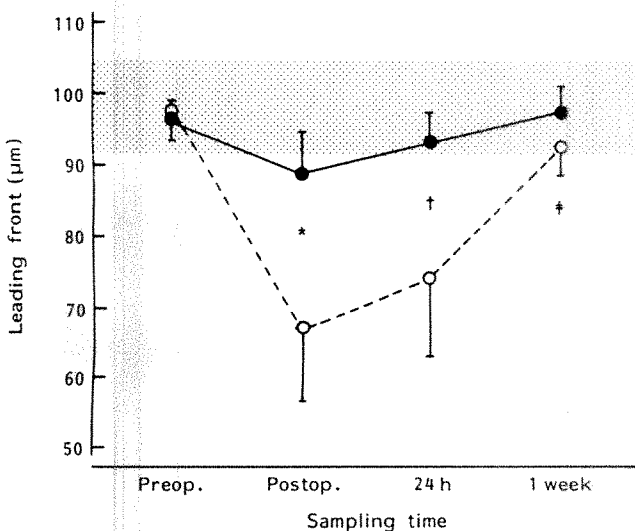


Figure 4 Changes in neutrophil migration towards human AB serum in patients undergoing major vascular surgery with (●) or without (○) aprotinin. Values are median (95 per cent confidence interval); the normal range is indicated by the shaded area. * $P < 0.001$; † $P < 0.002$; ‡ $P < 0.05$ (Mann-Whitney U test)

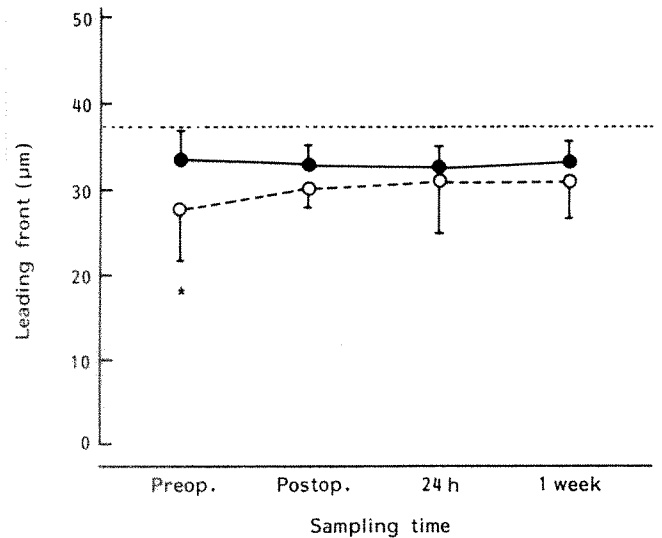


Figure 5 Changes in non-directed (towards buffer) neutrophil migration in patients undergoing major vascular surgery with (●) or without (○) aprotinin. Values are median (95 per cent confidence interval); the upper normal limit is indicated by the dotted line. * $P < 0.05$ (Mann-Whitney U test)

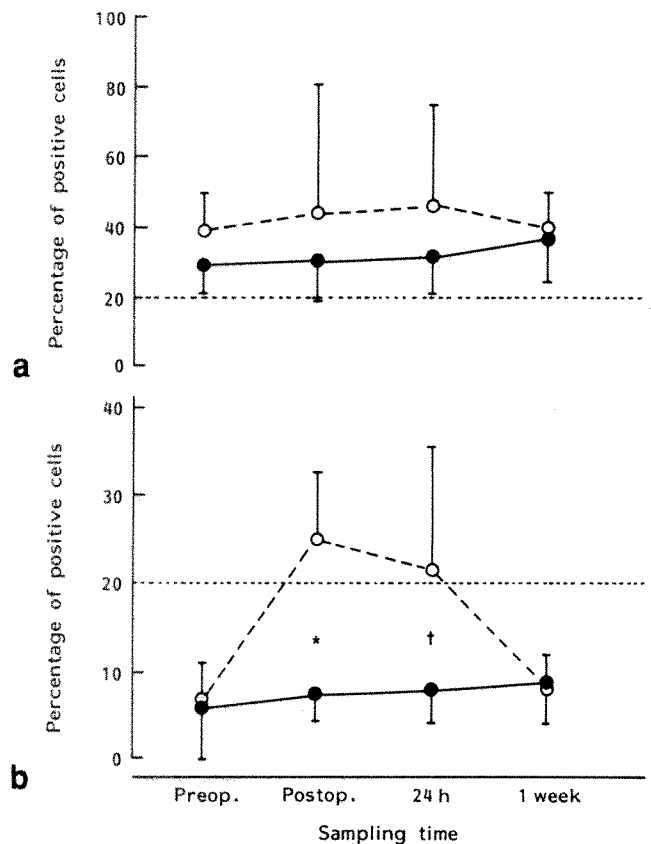


Figure 6 Changes in **a** stimulated and **b** unstimulated nitroblue tetrazolium reduction in patients undergoing major vascular surgery with (●) or without (○) aprotinin. Values are median (95 per cent confidence interval); the **a** lower and **b** upper normal limits are indicated by the dotted lines. * $P < 0.001$; † $P < 0.02$ (Mann-Whitney U test)

was significantly reduced in the control subjects immediately after surgery ($P < 0.001$) and 24 h after operation ($P < 0.002$). Furthermore, the BSF results at these times fell below the normal range. Aprotinin-treated patients, however, showed no significant fall in BSF and remained within normal limits throughout the operative period.

Compared with the aprotinin-treated patients, neutrophil migration towards FMLP was significantly reduced in the

controls at all times after surgery, falling below the normal range for this test immediately after operation (Figure 3). Although the aprotinin group showed a broadly similar pattern, this was not as marked and migration always remained within the normal range. Changes in migration towards AB serum were more dramatic. The control subjects showed a marked reduction in migration, this becoming distinctly abnormal immediately after surgery, and remaining so for at least 24 h. Compared with that in the aprotinin group, this reduction was statistically significant at all times after surgery (Figure 4). Neutrophils from aprotinin-treated patients, however, showed only a slight decrease in migration over the operative period, falling just below normal limits immediately after the operation. There was no significant change in non-directed migration after surgery in either group, although the controls had a significantly lower ($P < 0.05$) baseline value. Nevertheless, all results were within the normal range for this technique (Figure 5).

Neutrophils from aprotinin-treated patients showed no change in resting (unstimulated) NBT reduction during the period of observation (Figure 6b). In contrast, cells from controls showed a marked rise in NBT reduction to levels that were above the normal range, and significantly greater than those in patients receiving aprotinin, immediately ($P < 0.001$) and 24 h ($P < 0.02$) after surgery. NBT reduction after stimulation with a bacterial extract was unchanged, and remained within normal limits, throughout the period of observation in both groups (Figure 6a).

Discussion

The results of neutrophil function tests in the control patients generally confirm the changes in perioperative neutrophil function reported by others. These include increases in total white cell count²¹, reduction in intraneutrophilic granule proteins (indicating activation and release²²), reduced killing capacity²³, diminished chemotactic ability²⁴⁻²⁶, reduced superoxide production in response to FMLP or phorbol myristate acetate²⁷, and decrease in leukotriene B₄ production²². These defects may not all be directly attributable to surgery, however, because altered migrational ability, for example, may follow anaesthesia alone²⁴. For this reason, baseline samples were taken after induction of anaesthesia in both groups. Previous studies were either of relatively brief duration²⁴ or carried out on mixed groups of patients, including some with malignancy, where disturbances in neutrophil function might be expected²⁷. Duignan *et al.*²⁶ reported that chemotaxis was not significantly altered after surgery, although follow-up in this study was not until 5-8 days after operation. The present study suggests that neutrophil function has normalized by this time.

There are no previous reports of the effect of surgery on neutrophil BSF, although reduced oxidative responsiveness to FMLP, the stimulus used in this test, has been described²⁷. The BSF test permits the rapid assessment of neutrophil responsiveness and is relatively simple compared with tests of migration. Because neutrophils change shape during locomotion, BSF may be functionally related to the locomotor capacity of these cells¹⁷. The fact that BSF remains unimpaired in aprotinin-treated patients, unlike the controls, suggests that it is a useful way of assessing locomotive ability after operation. Neutrophil migration was normal towards FMLP and AB serum in the aprotinin-treated group, but was significantly impaired in the control patients. This supports the results of the BSF assay and agrees with data reported elsewhere^{24,28}. Taken together, the migration and BSF tests suggest that the ability to mobilize for movement and to migrate is better preserved in the aprotinin-treated patients than in the controls.

The results of the stimulated NBT reduction test in the aprotinin-treated patients were not significantly different from those in the controls, suggesting that the ability to respond fully to a bacterial stimulus was retained in the former group. These findings contrast with those of Utoh *et al.*²⁷, who found a

diminished superoxide response to FMLP on the first day after operation, although the heterogeneous group of patients studied may have contributed to this difference. In the unstimulated NBT tests, however, significantly lower results in the aprotinin-treated patients suggest that, unlike the controls, their neutrophils were not already engaged in superoxide production. Taken together, the NBT test results suggest that the mechanisms for superoxide production remain intact in the aprotinin-treated patients and that the activation of this granulocyte function by surgery is prevented by aprotinin. The serial leucocyte and differential counts give little additional information except that the expected physiological neutrophil mobilization²⁹ is not impaired in the aprotinin-treated group.

Whether alterations in results of leucocyte function tests in patients with a normal immune capacity affect perioperative morbidity or mortality rates remains to be established. This subject has been debated since 1903 when Snel³⁰ and Rubin³¹ showed that alterations in leucocyte function occurred under anaesthesia. More recently, Bruce and Wingard³² found no correlation between neutrophil function and morbidity, and there does not appear to be any relation between preoperative neutrophil function and postoperative sepsis^{26,28}. Neutrophils that are already stimulated and actively phagocytosing, or undergoing the respiratory burst, migrate relatively poorly (R. A. L., unpublished data) and the retention of the capacity to respond by both activation and migration seen in aprotinin-treated patients may be advantageous. There is no evidence that this would be detrimental to the patients' perioperative course.

There is no obvious explanation for the reduction in neutrophil activation during surgery in the aprotinin-treated patients. Damage to endothelial cells and release of platelet-derived products can activate neutrophils³³ and a platelet-protective effect may thus inhibit neutrophil activation. Activated components of the haemostatic and complement pathways may contribute. Kallikrein can activate neutrophils and release neutrophil elastase^{34,35}. Aprotinin is a weak inhibitor of this enzyme¹, and plasma levels of elastase are lower in patients undergoing cardiopulmonary bypass treated with aprotinin². This probably reflects lower levels of neutrophil activation rather than direct enzyme inhibition, as *in vitro* studies have shown that extracorporeal circulation, especially with bubble oxygenators, can greatly increase plasma elastase levels. As neutrophil elastase is thought to be an alternative pathway of fibrinolytic activation^{36,37} and hyperfibrinolysis appears to play a role in the pathogenesis of surgical bleeding³⁸, such an effect may help to explain the haemostatic properties of aprotinin. The interaction between enzymes and other mediators of the inflammatory response is complex³⁹ and there may be many sites at which a proteolytic inhibitor could inhibit neutrophil activation.

These results show that aprotinin normalizes leucocyte function after major surgery. It seems unlikely, given the good response in the migration and NBT tests, that any potential leucocyte response is impaired. Many patients, especially those undergoing cardiac surgery, have been treated with high-dose aprotinin. There do not appear to be any harmful effects attributable to the effects of aprotinin on leucocyte function such as increased septic or thromboembolic complications. This study confirms, albeit in a limited number of patients, that aprotinin can be given as a haemostatic agent without inhibiting neutrophil function. The apparent preservation of neutrophil function may be of clinical benefit, although larger studies would be needed to confirm this suggestion.

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Gastrointestinal tract perforation in children due to blunt abdominal trauma

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Over a 14-year period 587 children under 13 years of age were admitted with blunt injury to the abdomen. Twenty-nine (4.9 per cent) of these were found to have bowel rupture. Evidence of peritonitis was present at initial evaluation in 11 children (38 per cent). Radiological evidence of perforation (pneumoperitoneum) was present in only five of 27 (19 per cent) with a further six of 27 (22 per cent) showing dilated loops of bowel or fluid levels. Thus 59 per cent of radiographs were not diagnostic. The mean time from admission to laparotomy was 17 h. Proximal bowel perforation was common and perforation at multiple sites occurred in five patients; 59 per cent had a concomitant injury which resulted in two deaths (from head injury). Initial clinical and radiological evidence of bowel perforation can be misleading and reliance on such indicators may result in significant diagnostic delay. Frequently repeated clinical examination is advocated; progression of abdominal signs should alert the clinician to proceed to laparotomy.

Blunt abdominal trauma in children causing liver and spleen injury can be successfully managed in most cases without surgery^{1,2}. However, such trauma may also cause bowel rupture, either in isolation or together with other visceral injuries, and in these cases emergency surgery is indicated. Diagnosis of gastrointestinal tract perforation remains difficult and delay in diagnosis may result in increased morbidity rates. Dickinson *et al.*³ and Kovacs *et al.*⁴ stressed both the lack of special investigations which might help formulate management policy, and the importance of interpretation of abdominal signs by the attending surgeon.

Patients and methods

During the period 1977–1990, 587 children with blunt abdominal trauma were admitted to the trauma unit at this hospital. In 197 children no specific injury was found, in 29 (4.9 per cent) there was gastrointestinal tract rupture, and in 361 a further 701 visceral injuries were documented¹. In this paper the 29 children with gastrointestinal tract perforation are reviewed with special reference to the pattern of injury, value of radiology and factors which contributed towards diagnostic delay.

Results

The mean age of the 29 children was 7 years 3 months (range 9 months to 12 years). The causes of injury are shown in Table 1. On initial examination none of the patients was in hypovolaemic shock. Abdominal distension was present in 50 per cent, but clinical evidence of peritonitis as shown by generalized guarding with rebound tenderness was present in only 11 patients (38 per cent), and bowel sounds were recorded as normal in four of 26 (15 per cent). Analgesia was withheld if the abdominal examination was equivocal; once a decision to operate had been taken, intravenous morphine sulphate was commenced and continued after operation. Special investigations performed on admission included chest and abdominal radiography in 27 children and serum amylase measurement in 6. The results of these investigations are presented in Table 2. Peritoneal lavage was not performed. A pneumoperitoneum was present in five children (19 per cent) although a further six (22 per cent) had radiographic features suggestive of intra-abdominal pathology, such as free fluid or dilated loops of bowel with air–fluid levels. Abdominal computed tomography (CT) was performed in only two cases to rule out

solid organ injury. In one of these a ruptured jejunum was identified by leakage of oral contrast; the other scan, despite indicating increased intra-abdominal fluid, showed no features of bowel perforation. The serum amylase level was significantly raised in five children (31 per cent). Associated injuries are listed in Table 3.

The mean delay between admission and surgery was 17 (range 2–144) h. The indication for laparotomy was increasing

Table 1 Aetiology of blunt abdominal trauma causing hollow viscus perforation in 29 patients

Motor vehicle accident	
Pedestrian	12
Passenger	3
Assault	5
Fall	4
Struck by object (horse, swing, pillar)	3
Crush	2

Table 2 Initial investigations before operation

	Total number	Positive
Pyrexia (temperature > 37.5 °C)	28	4 (14)
Free air on chest or abdominal radiography	27	5 (19)
Raised serum amylase (more than three times normal level)	16	5 (31)

Values in parentheses are percentages

Table 3 Associated injuries in 17 of 29 patients

Head injury	8
Laceration of liver and/or spleen	7*
Fractured pelvis	7*
Fractured lower limb	4
Pancreatitis	4*
Ruptured diaphragm	2*

*Evidence of local force

Table 4 Site of gastrointestinal perforation and operative procedures in 29 patients

Site	
Jejunum	18
Ileum	7
Stomach	5
Duodenum	1
Colon	1
Multiple	5
Surgical procedure	
Oversewing/simple closure	20 (69)
Resection and anastomosis	9 (31)

Values in parentheses are percentages

abdominal tenderness, with or without signs of peritonitis. Positive radiological findings provided further indication for laparotomy in 11 patients (41 per cent). Intravenous antibiotics (penicillin, aminoglycoside and metronidazole) were given at induction of anaesthesia, and continued for a period of 5 days after operation. Intraoperative cephalosporin at a concentration of 2 mg ml⁻¹ in normal saline was used to irrigate the peritoneal cavity. The sites of injury and the procedures performed at laparotomy are presented in Table 4. The majority of ruptures occurred in the proximal bowel and were satisfactorily repaired by trimming of ragged borders and closure of the perforation.

A further seven children with increasing abdominal tenderness were operated on for suspected peritonitis but were found to have no perforation at laparotomy. In only two of the seven patients was no pathology found; in the remaining five injuries included two retroperitoneal haematomas, two splenic lacerations, and one traumatic pancreatitis.

Two patients (7 per cent) died, both from an associated head injury which was complicated in one case by respiratory distress syndrome and disseminated intravascular coagulation. Complications after operation occurred in ten children: intestinal obstruction requiring surgical intervention (three cases) and intra-abdominal infection (two cases) were the local sequelae; other problems included pneumonia, atelectasis and pleural effusion (three cases), transient renal failure (one case) and femoral vein thrombosis related to a fractured pelvis and femoral artery repair (one case). Patients were discharged a mean of 18 days after admission.

Discussion

Of 587 children with a history of blunt abdominal trauma 29 (4.9 per cent) sustained a gastrointestinal tract perforation. This incidence was considerably lower than that of other visceral injuries, namely to the liver ($n = 224$), spleen ($n = 96$), and kidney ($n = 333$)¹. Management of paediatric trauma victims after resuscitation is initially conservative and surgical exploration is necessary only in a minority – less than 13 per cent in this series¹.

The increased and incorrect use of restraining car seat belts has been correlated with a greater incidence of bowel injury⁵, and child abuse must always be considered as a possible cause where the history and presenting features do not tally. It has been stated that the fixed portions of the bowel (e.g. duodenojejunal flexure and ileocaecal area) are most at risk⁶, but in the present series this was not the case. The site of the bowel exposed to direct force was where the rupture occurred – in the proximal small bowel in more than two-thirds of cases. This may be due to the relatively thin and often protuberant abdominal wall of the child.

Initial clinical examination may be misleading and only 50 per cent of patients were considered to have serious intra-abdominal pathology. Special investigations also do not play a pivotal role in confirming the diagnosis and proved unreliable, especially in the early stages. Abdominal radiographs are reported to show free air in under 50 per cent of

cases^{3,7}, and did so in only 19 per cent of patients in the present series, although other non-specific features such as dilated loops of bowel or free intraperitoneal fluid were present in a further 22 per cent. A left lateral decubitus view may show free intraperitoneal air⁷ and specific radiological techniques may increase the yield, giving only three of 24 false-negative results in one series⁸. Abdominal CT with oral contrast medium may be a valuable investigation for excluding hollow viscus rupture. Donohue *et al.*⁹ reported 13 of 14 positive diagnoses on CT, but other authors have not matched this diagnostic accuracy, with a range varying from 47 to 65 per cent^{10,11}.

Laboratory investigations have also proved unreliable in confirming the diagnosis. Significantly raised serum amylase levels occurred in only five (31 per cent) of the 16 patients for whom they were measured; a normal level does not exclude bowel perforation⁴. Peritoneal lavage has been advocated as a reliable method of confirming intestinal perforation, with an accuracy of over 90 per cent in the blunt trauma victim quoted by McLellan *et al.*¹². However, routine peritoneal lavage is not practised at this institution as the presence of intraperitoneal blood *per se* is not an indication for surgery, its accuracy is not sufficient (especially in the early stages) and subsequent clinical evaluation becomes more difficult. It may be of particular benefit when tenderness cannot be adequately evaluated, e.g. in the unconscious patient. Laparoscopy may also offer advantages for the early diagnosis of bowel rupture.

Repeated clinical examination, preferably by the same surgeon at intervals of 2–4 h, provides the most reliable indicator of significant intra-abdominal pathology; progressive deterioration should alert the clinician to underlying bowel perforation. Surgery consists of a full laparotomy and inspection of the total extent of the gastrointestinal tract to exclude the multiple sites of perforation seen in 17 per cent of children in this series. Simple debridement and oversewing is performed if possible, but resection and anastomosis may be necessary for more extensive injuries.

Associated injuries are the major cause of morbidity and even death in blunt trauma victims¹³; 59 per cent in the present series had associated injuries. Of significance was the damage done by the force to adjacent sites (fractured pelvis, lacerated liver or spleen and ruptured diaphragm). Two patients died, both with an associated head injury. No deaths were specifically attributable to diagnostic delay – on average 17 h – although a threshold of 12 h has been suggested as significant to decrease the rate of complications⁶.

Intestinal rupture secondary to blunt abdominal trauma is less common in children than in adults¹⁰. Routine special investigations do not offer the 'fast route' to early diagnosis of gastrointestinal tract perforation. Rather, repeated clinical evaluation of the abdomen, preferably by the same surgeon, remains the most reliable way of reaching an early diagnosis.

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Use of a suprapubic catheter for laparoscopic cholangiography

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The advent of laparoscopic cholecystectomy has presented the surgeon with new technical challenges. Although this operation is now well established, the role of laparoscopic cholangiography is still not clearly defined. Opinion is divided as to whether cholangiography should be performed routinely or reserved selectively for patients with clinical or biochemical evidence of common bile duct stones¹⁻⁴. While peroperative visualization is superior to standard cholecystectomy, the high incidence of bile duct anomalies and inadequate dissection of the common duct ensures that the potential for bile duct injury remains. Cholangiography minimizes this risk by clarifying any uncertainties regarding anatomy and indicating whether iatrogenic injury has occurred. Unsuspected common bile duct stones occur in up to 10 per cent of standard cholecystectomies. Routine cholangiography would identify these cases, allowing stone removal after operation via endoscopic sphincterotomy or abandonment of the procedure in favour of open exploration.

Various methods of laparoscopic cholangiography have been described³⁻⁶ which involve the use of catheters introduced and manipulated into the cystic duct using grasping forceps, or the use of custom-made and expensive cholangiocatheters.

Surgical technique

In an effort to overcome protracted, difficult and sometimes futile attempts to cannulate the opened cystic duct using forceps-held catheters, this unit has begun to use a suprapubic catheter (Boonano; Becton-Dickinson, Rutherford, New Jersey, USA) during cholangiography for cystic duct cannulation. The catheter (18 Fr trocar, 14 Fr cannula) is introduced under direct camera vision by a separate puncture in the right hypochondrium. The trocar is >20 cm long, making the cystic duct easily accessible from virtually any position in

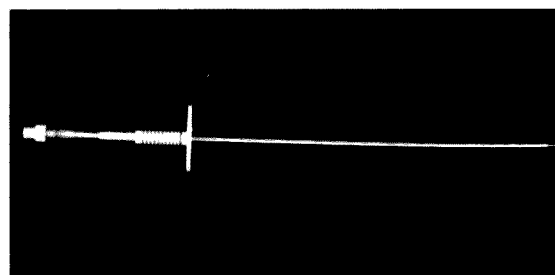


Figure 1 Catheter measures 20 cm and curves on removal of trocar

a patient of any size (Figure 1). The catheter tip curves naturally as the trocar is removed, facilitating positioning in the duct. The tip of the catheter is manipulated under camera vision, using the trocar from outside the abdomen, to the opening fashioned in the cystic duct. The trocar is gently retracted as the tip is advanced into the cystic duct (a distance of 3 cm to include all lateral drainage holes). With the cannula in position, the trocar holds the catheter rigidly in position intra-abdominally until it can be safely fixed within the duct by ligature clips. The trocar can then be removed and operative cholangiography performed through the catheter.

This technique is safe, simple and uses inexpensive and readily available equipment. It may shorten the procedure of peroperative cholangiography during laparoscopic cholecystectomy by obviating the need for manipulation of catheters using grasping forceps.

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Effect of antibiotics in fibrin sealant on healing colonic anastomoses in the rat

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In 90 rats a colonic anastomosis was constructed with 12 interrupted 7/0 polypropylene sutures. Group 1 (n = 30) served as a control group. In group 2 (n = 30) the anastomosis was sealed with fibrin adhesive and in group 3 (n = 30) a mixture of fibrin, clindamycin and cefotaxime was used. On days 2, 4 and 7, ten animals in each group were killed. Adhesion formation was significantly increased in groups 2 and 3 compared with the control group. On day 2 the anastomosis was significantly stronger after sealing with antibiotic–fibrin mixture. On day 4 the bursting pressure in group 2 was significantly lower than in groups 1 and 3. At the same time the concentration of hydroxyproline was significantly reduced in group 2, but not in group 3. The addition of antibiotics prevents the negative effect of fibrin adhesive on the healing colonic anastomosis and contributes to a stronger anastomosis on day 2 after operation.

Leakage from colonic and rectal anastomoses has a reported incidence of up to 50 per cent¹ and is associated with significantly increased mortality and morbidity rates². Fibrin sealant is a multicomponent biological adhesive made from concentrated human fibrinogen which can be used to establish haemostasis or as an adhesive in wound repair. Additional sealing with fibrin sealant has been advocated in normal and high-risk colonic anastomosis to prevent anastomotic leakage^{3–7}. Experimental studies provide conflicting results and prospective, randomized clinical studies are lacking^{8,9}. A negative influence of additional fibrin sealant on the healing colonic anastomosis has recently been demonstrated in the rat¹⁰. This negative effect might be caused by an increased inflammatory reaction near the anastomosis^{9,10}.

The quantity and quality of collagen in the submucosal layer of the intestinal wall determines the strength of the healing intestine¹¹. After colonic anastomosis there is first a period of breakdown of collagen, followed by synthesis^{12–14}. Collagen is highly resistant to proteolytic agents but is readily degraded by collagenase. Factors directly influencing the activity of collagenase are infection and inflammation around infected anastomoses^{15,16}. Bacteria and inflammatory cells are known to produce collagenase^{17,18}. As every colonic anastomosis must be considered to be contaminated by intestinal bacteria, the fibrin clot will be infected too. It is possible to mix antibiotics with fibrin glue without impairment of its adhesive and clotting properties. High local antibiotic concentrations are then slowly released from the fibrin clot¹⁹.

This study was designed to determine whether the addition of antibiotics abolishes the negative effect of fibrin sealing on the strength and collagen metabolism of healing colonic anastomoses in the rat.

Materials and methods

Ninety male Wag/Rij rats, weighing 180–230 g, were randomly allocated to three treatment groups and were allowed water (acidified, pH 3.0) and food (AM II; Hope Farms, Woerden, The Netherlands) *ad libitum* before and after operation. Using ether anaesthesia and through a midline incision, 1 cm of the left colon, 3 cm proximal to the peritoneal reflection, was resected. A single-layer end-to-end anastomosis was performed with 12 interrupted, inverting 7/0 polypropylene (Prolene; Ethicon, Norderstedt, Germany) stitches in a standard fashion. The resected segment of colon was frozen and kept at –80°C until analysis, to serve as an individual control. The experimental groups were: group 1, control sutured anastomosis; group

2, sutured anastomosis plus human fibrin sealant; group 3, sutured anastomosis plus fibrin–antibiotic complex. The human fibrin sealant (Tissucol; Immuno AG, Vienna, Austria) was prepared according to the manufacturer's instructions. The sealant consists of a freeze-dried protein concentration of human fibrinogen (120 mg/ml) which is reconstituted in a solution of aprotinin (3000 kallidinogenase inactivator units/ml) and a solution of thrombin (500 units/ml) and calcium chloride (40 mmol/l). In treatment group 3, 1 ml thrombin solution was mixed with 50 mg cefotaxime and 50 mg clindamycin. After preheating to 37°C the components were reconstituted in their solutions and drawn up in separate syringes. On mixing and application the fibrinogen was activated to form fibrin and the solution was transformed into a rubber-like adhesive mass. The fibrin–antibiotic complex contains 25 mg cefotaxime and 25 mg clindamycin per ml fibrin glue. For one anastomosis 0.2 ml fibrin sealant was used. On days 2, 4 and 7, ten rats from each group had the laparotomy incision reopened under ether anaesthesia and the degree of adhesion formation was assessed: 0, no adhesions; 1+, minimal adhesions, mainly between anastomosis and omentum; 2+, moderate adhesions, i.e. between omentum and the anastomotic site and between the anastomosis and a loop of small bowel; 3+, severe and extensive adhesions, including abscess formation⁹. The rectum was then cannulated and the left colon was ligated twice, 1 cm proximal and 1 cm distal to the anastomosis, the latter around the rectal cannula. Care was taken not to disrupt the anastomosis and its adhesions. The rectal cannula was connected to an infusion pump (Hospal; Dasco Spa, Medolla, Italy), with a side arm to a pressure transducer connected to a recorder. The *in vivo* anastomotic bursting pressure was measured by infusing normal saline at a constant rate of 1 ml/min, and was marked by an abrupt loss of pressure. After measuring the bursting pressure the animal was killed. The left colon, including the anastomosis, was excised and dissected free of mesenteric fat. Three rings of colon tissue 0.5 cm wide were cut: one ring of tissue containing the anastomosis, one ring proximal and one ring distal to the anastomosis. For histological examination a small segment of the anastomotic ring was cut and placed in 4 per cent formaldehyde. The remaining tissue samples were immediately frozen and kept at –80°C for hydroxyproline assay.

Hydroxyproline was determined using a modified version of the colorimetric assay of Stegeman *et al.*^{20,21}.

Collagen concentrations were calculated in micrograms per milligram dry weight. The collagen concentration of the control colon was used to calculate any change in collagen content.

Sections of 5-µm thickness were cut and stained with haematoxylin and eosin. A periodic acid–Schiff, a Gomori and a Weigert–van Gieson stain were used to assess the tissue reaction. The inflammatory infiltrate (neutrophils, eosinophils, macrophages) and tissue organization (fibroblast and capillary proliferation) were scored semiquantitatively as follows: +, numerous; ±, occasionally present; –, absent.

For statistical analysis the mean values and the standard error of the mean (s.e.m.) were calculated. Results were compared using one-way analysis of variance (ANOVA) with the Student–Newman–

Keuls test, χ^2 test and Fisher's exact test where appropriate. The null hypothesis of no difference was rejected at a *P* value of 0.05.

Results

All rats survived and no animal showed macroscopic evidence of leakage from the anastomosis. There were no differences in change of body-weight.

The results of adhesion formation are presented in Table 1. Adhesion formation was more extensive in groups 2 and 3 compared with group 1 by day 4. No animal showed abscess formation.

The results of anastomotic bursting pressure measurements are presented in Figure 1. On day 2 bursting invariably occurred at the anastomosis. On day 4, 80 per cent of bursting in the control group occurred at the anastomosis; in groups 2 and 3 rupture without exception took place at the suture line. On day 7 the rupture invariably occurred outside the anastomosis in groups 1 and 3; in one animal in group 2 the anastomosis was the place of rupture. Bursting was most likely to take place proximal to the anastomosis in 80, 70 and 90 per cent of animals

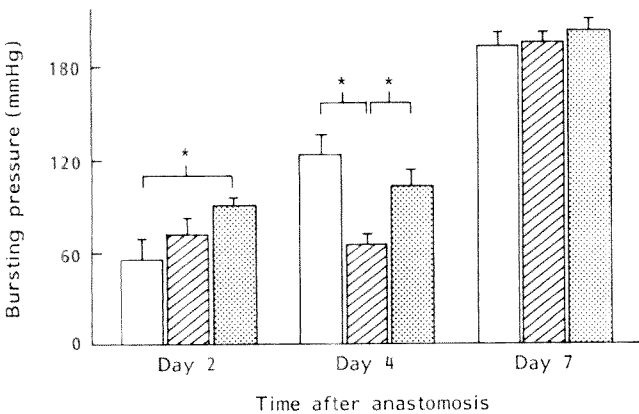


Figure 1 Colonic bursting pressure on days 2, 4 and 7 after creation of an end-to-end anastomosis. Values are mean(s.e.m.); n = 10. □, Control; ▨, fibrin sealant; ▤, fibrin sealant plus antibiotics. **P* < 0.05 (ANOVA and Newman-Keuls test)

in groups 1, 2 and 3, respectively. On day 7 the colon wall was significantly weaker proximal to the anastomosis compared with the distal colon (*P* < 0.01).

The values of collagen concentration around the anastomosis and relative change compared with individual normal values are presented in Table 2. Hydroxyproline concentration was lowest on day 2 in all groups. The relative loss of collagen was prominent in all groups on most occasions. Overall there were slight differences in relative collagen loss between groups 1 and 3; these changes became statistically significant only on day 7. Figure 2 illustrates the relative change of collagen around the anastomosis.

Histological examination showed remnants of fibrin glue outside the anastomosis on days 2 and 4 (Figure 3); on day 7, however, this fibrin was not demonstrated. On days 2 and 4 the fibrin sealant in groups 2 and 3 was heavily infiltrated and surrounded by neutrophilic granulocytes. On day 4 this neutrophilic infiltrate was more pronounced in group 2 than in group 3 (Figure 4). The intestinal wall showed an infiltration of neutrophilic and eosinophilic granulocytes and macrophages. Apart from the number of neutrophils, no clear differences could be found between the treatment groups.

On day 2 fibroblasts were present only occasionally. On days 4 and 7 macrophages and fibroblasts were abundant in all groups, while granulocytes had reduced in number again. No differences were noted concerning the number of fibroblasts and capillary proliferation.

Discussion

Fibrin sealant contributes to wound healing by producing local haemostasis and by stimulating the influx of macrophages which produce factors that cause angiogenesis, fibroblast proliferation and collagen production²²⁻²⁵. Additional sealing has been advocated for normal and high-risk colonic anastomoses in patients to prevent anastomotic leakage³⁻⁷. In the rat model, however, application of human and rat fibrinogen has a negative effect on the healing colonic anastomosis¹⁰. Since anastomoses are contaminated and fibrin is a culture medium for pathogens, antibiotics in the adhesive may prevent infection. Clindamycin and cefotaxime can be added to fibrin adhesive without impairing its clotting behaviour⁹.

Table 1 Adhesions of colonic anastomoses in the rat

Group	n	Day 2				Day 4				Day 7			
		0	1+	2+	3+	0	1+	2+	3+	0	1+	2+	3+
1 (Control)	30	0	6	4	0	0	9	1	0	0	6	4	0
2 (Fibrin sealant)	30	2	3	5	0	1	3	6	0*	0	6	4	0
3 (Fibrin sealant and antibiotics)	30	0	4	4	2	0	0	3	7*	0	2	5	3

**P* < 0.05 (group 1 versus groups 2 and 3, χ^2 test)

Table 2 Concentration and relative change of collagen in colonic anastomoses in the rat

Site	Group	Day 2	Day 4	Day 7
Proximal to anastomosis	1	91(8) (−49)	109(7) (−29)*	158(11) (−7)*
	2	82(5) (−50)	85(9) (−47)	102(4) (−38)
	3	68(6) (−48)	81(4) (−32)	92(5) (−5)
Anastomosis	1	97(6) (−44)	113(6) (−26)*	152(7) (−11)
	2	77(6) (−52)	81(9) (−49)	139(3) (−15)*
	3	67(3) (−48)	80(4) (−32)	106(6) (+8)
Distal to anastomosis	1	135(10) (−22)	146(7) (−6)*	157(11) (−8)*
	2	131(6) (−19)	130(5) (−19)	144(3) (−11)
	3	98(6) (−26)	102(4) (−15)	113(7) (+15)

Values are mean(s.e.m.) expressed in micrograms per milligram dry weight; values in parentheses are the relative percentage changes compared with the individual control value. **P* < 0.05 (day 4: group 1 versus group 2; day 7: proximal, group 1 versus group 2; anastomosis, group 2 versus group 3; distal, group 1 versus group 3; ANOVA and Newman-Keuls test)

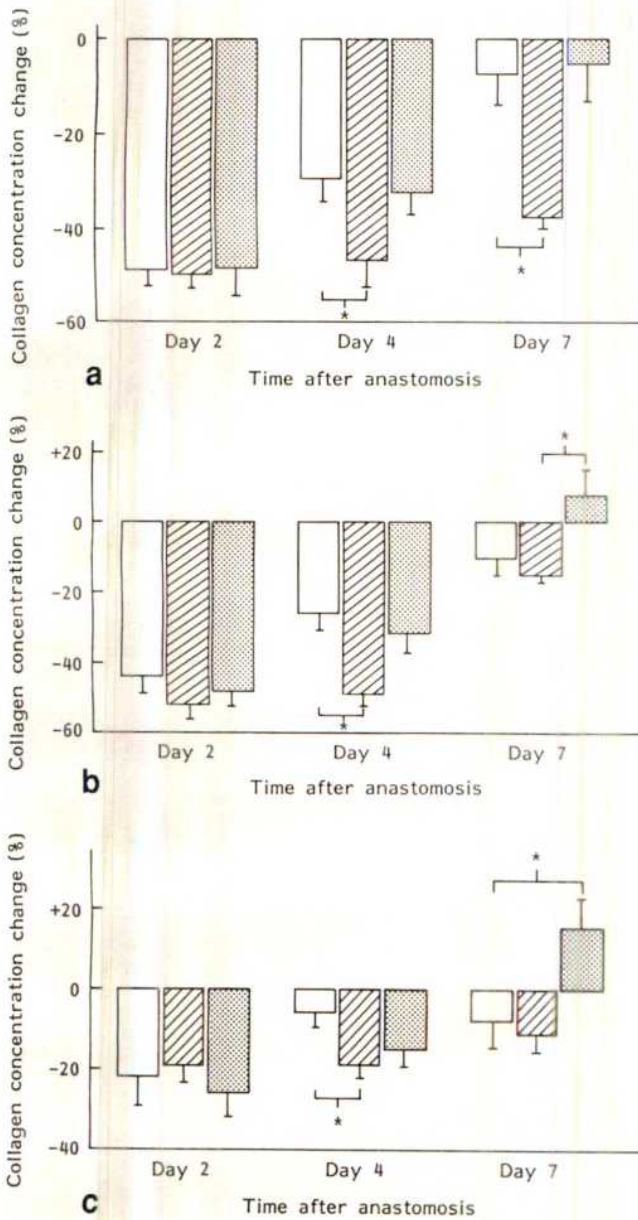


Figure 2 Relative changes in collagen concentrations **a** proximal to colonic anastomosis; **b** in colonic anastomotic area; **c** distal to colonic anastomosis. Values are mean (s.e.m.) percentage changes compared with preoperative values; $n = 10$. □, Control; ▨, fibrin sealant; ▩, fibrin sealant plus antibiotics. * $P < 0.05$ (ANOVA and Newman-Keuls test)

The application of fibrin sealant resulted in increased adhesion formation around the anastomosis on day 4. This was more prominent after addition of antibiotics. On day 7 this difference was not present. Others have found that fibrin glue prevents adhesion formation to peritoneal-muscular defects²⁶. A possible explanation for the difference may be the presence of colonic bacteria in this model.

On day 2 the bursting pressure was significantly higher after sealing with antibiotic-fibrin complex. This did not correlate with diminished collagen degradation, and may be caused by mechanical bonding properties of the adhesive. Addition of antibiotics might inhibit degradation of the fibrin clot during the first few days and improve the adhesive property.

Application of fibrinogen produced a lower bursting pressure on day 4, but this was prevented by addition of antibiotics to the fibrin sealant. In group 2 the lower bursting pressure on day 4 correlated with reduced collagen concentration. This decreased collagen concentration may account for the lower bursting pressure because bursting pressure is dependent mainly on submucosal collagen¹⁴.

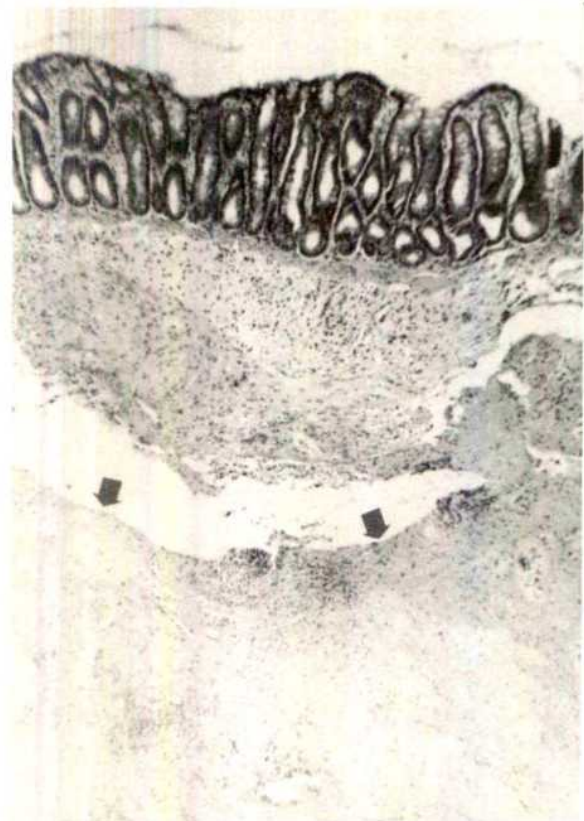


Figure 3 Histological section on day 4 after operation of a fibrinogen-sealed colonic anastomosis (arrows). The submucosa and fibrin sealant show cellular infiltrate. (Haematoxylin and eosin stain, original magnification $\times 80$)

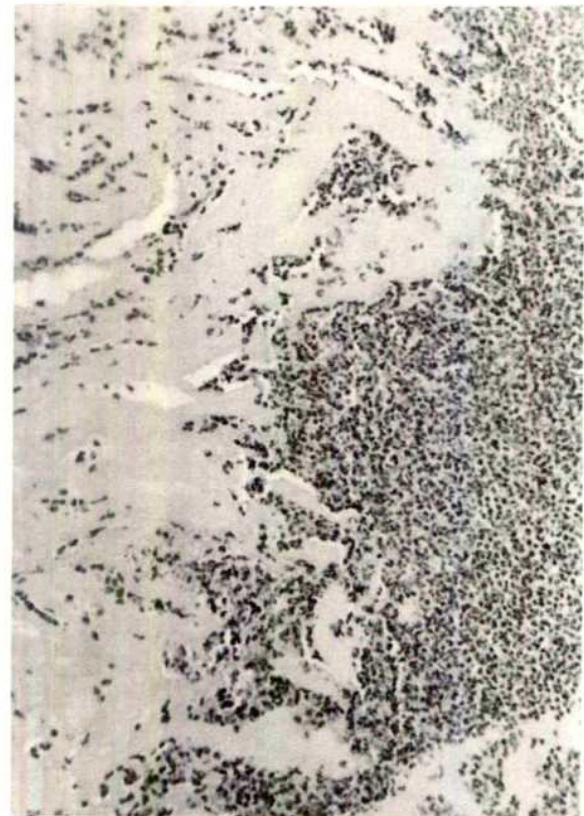


Figure 4 Detail of fibrin sealant showing massive cellular infiltrate of mainly neutrophilic granulocytes. (Haematoxylin and eosin stain, original magnification $\times 160$)

Addition of antibiotics to the sealant gave almost the same hydroxyproline values on day 4 as in control animals. The reduced degradation of collagen after addition of antibiotics may be explained by reduced bacterial infection and inflammatory reaction. On day 4 the neutrophilic infiltration of the anastomoses with antibiotic-fibrinogen was significantly reduced.

On day 7 the net hydroxyproline change in the anastomotic segment as well as distal to it was positive and significantly higher in group 3. This did not result in a higher bursting pressure. At this time the intestine is weakest proximal to the anastomosis, as shown by the point of disruption. On day 7, therefore, bursting pressure is not a good measure of anastomotic collagen concentration. The finding of asymmetrical collagen changes around the anastomosis has been reported in other studies^{14,27}. This study demonstrated that collagen changes were more marked proximally and explains why the rupture occurred almost exclusively proximal to the anastomosis on testing the bursting pressure on day 7. No explanation for this pattern of collagen distribution can be found.

Histological examination showed excessive accumulation of neutrophilic granulocytes in the fibrin sealant covering the anastomosis on days 2 and 4. Fibrinogen gives rise to infiltration of granulocytes and local fibrin deposition may predispose to local infection and inflammation. Under normal conditions, deposition of fibrin occurs within 3 h and the wound is infiltrated by granulocytes, followed by macrophages²⁸ during the first 24 h. Foreign material, e.g. fibrin, prolongs the inflammatory phase and provides a favourable site for bacterial proliferation. A significant reduction in the lowering of hydroxyproline concentration around the anastomosis was observed by Mastboom *et al.*²⁹ using germ-free rats. The results of the present study with antibiotics suggest that local bacterial infection contributes to collagen degradation following the construction of a colonic anastomosis.

Neutrophilic granulocytes and bacteria are sources of proteolytic enzymes including collagenase and may cause increased collagen breakdown in the intestinal wall. The postoperative decrease of breaking strength of colonic anastomoses is not apparent in rats with neutropenia³⁰. In this model the increased number of neutrophils at the site of the anastomosis is responsible for the increased loss of hydroxyproline in the colonic wall following the addition of fibrin sealant. The results do not show enhanced healing of colonic anastomosis following sealing with fibrin glue, contrary to some other studies³⁻⁷. Addition of antibiotics to the fibrin sealant improved the mechanical properties of the anastomosis on day 2 and abolished the decrease in bursting pressure on day 4. The addition of antibiotics may be useful in the clinical application of fibrin sealant.

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Functional evaluation of the intrathoracic stomach as an oesophageal substitute

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A study of duodenogastric reflux and gastric function was undertaken in 16 patients 1–7 years after oesophagectomy and high intrathoracic oesophagogastrostomy for oesophageal carcinoma. All were able to eat satisfactorily; ten complained of mild foregut symptoms and ten had endoscopic mucosal lesions. Biliary excretion scintigraphy demonstrated pathological duodenogastric reflux in 11 patients. The emptying of a semisolid radiolabelled meal from the intrathoracic stomach in the upright position was significantly quicker than in control subjects ($P < 0.01$). No gastric motor activity was recorded on manometry, suggesting that the transposed stomach acts like an inert tube. Results of 24-h pH monitoring showed that the area under the curve at $\text{pH} < 4$ in the stomach was significantly less than in control subjects ($P < 0.001$). In addition, patients had a significantly greater oesophageal alkaline exposure ($P < 0.001$). The vagotomized intrathoracic stomach therefore empties well in the upright position, but is subjected to reflux of alkaline duodenal contents and can retain the ability to produce acid. The interaction between alkaline and acid contents in the pathogenesis of symptoms and mucosal lesions needs further investigation.

Oesophageal replacement using the stomach is a well established method of reconstruction of the alimentary tract after oesophagectomy for cancer¹. As experience has been gained with this operation over the years, it has become clear that performing the oesophagogastric anastomosis high in the chest can markedly reduce the incidence of troublesome reflux symptoms. In addition, most surgeons have routinely added pyloromyotomy or pyloroplasty to prevent gastric stasis secondary to the incidental truncal vagotomy^{2,3}.

However, in spite of the early satisfactory results, some patients complain of discomfort during or shortly after eating, and dysphagia may occur in up to 50 per cent of cases⁴. A study in long-term survivors has shown a 62 per cent incidence of postoperative symptoms, although 84 per cent of patients were able to maintain a normal diet and 87 per cent could return to work⁵.

The purpose of the present study was to investigate the pathophysiology of the intrathoracic stomach used as an oesophageal substitute, in an attempt to correlate objective findings with foregut symptoms after operation.

Patients and methods

Patients

The population studied was drawn from a group of 30 randomly selected patients who had undergone oesophagectomy and high intrathoracic oesophagogastrostomy for squamous cell carcinoma of the thoracic oesophagus in this department between 1980 and 1989. Eleven of the 30 patients (37 per cent) complained of foregut symptoms after operation. Overall, only 16 of the 30 patients agreed to participate in the study, which was carried out over a 6-month period (May–October 1990).

There were 13 men and three women, with a median age of 59 (range 46–75) years. The operation consisted of a right-sided transthoracic oesophagectomy using the stomach as an oesophageal substitute. A large isoperistaltic tube was fashioned by resection of the lesser curvature with the GIA (US Surgical, Norwalk, Connecticut, USA) stapler applied two or three times. Digital disruption of the pylorus was performed routinely by invagination of the distal stomach into the pyloric lumen. The stomach was then placed in the posterior mediastinum and the oesophagogastric anastomosis fashioned at a level between the azygos vein and the apex of the chest using a circular

stapler (EEA25 or 28; US Surgical). Postoperative tumour staging by the tumour node metastasis (TNM) classification was $T_{1-2}N_0M_0$ in ten patients, and $T_{2-3}N_1M_0$ in six cases.

At the time of examination, 1–7 years after surgery, none of the patients had received adjuvant therapy and none had signs of tumour recurrence. All individuals had a Karnofsky index > 80 , and were able to eat between three and five meals daily without difficulty. Twelve patients (75 per cent) had continued to drink alcohol and/or smoke after operation: daily mean (s.d.) alcohol intake was 114 (65) g, and the daily mean (s.d.) number of cigarettes smoked 19 (11).

Postoperative foregut symptoms were present in ten (62 per cent) of the 16 patients: heartburn and/or regurgitation in nine cases and early dumping in one. One patient also complained of intermittent diarrhoea. Symptoms were usually mild and responsive to H_2 -receptor antagonists and dietary adjustments. Changes in body-weight occurred after operation in only three patients, who lost 2, 4 and 8 kg.

At the last endoscopic examination all patients had a patent oesophagogastric anastomosis and no evidence of stasis in the intrathoracic stomach. Mucosal lesions were found in ten patients (62 per cent), oesophagitis in five, gastritis in three and gastric ulcer in two. Three of these patients were asymptomatic.

The functional studies consisted of biliary excretion scintigraphy, gastric emptying scan, manometry and 24-h oesophageal and gastric pH monitoring. The studies were performed in hospital after an overnight fast. Patients were requested not to smoke or take drugs for at least 3 days before the tests.

Radioisotope studies

Biliary excretion scintigraphy was performed after oral administration of 4 g dried egg yolk and 10 g sorbitol. A total of 200 MBq ^{99m}Tc -di-isopropyliminodiacetic acid (DISIDA) was injected intravenously. The patient was positioned supine under a γ camera equipped with a low-energy, general-purpose collimator. A series of 60 1-min images was acquired in a 64×64 byte mode matrix. The patient was asked to drink, in a single swallow, 10 ml water containing 20 MBq ^{99m}Tc -DISIDA while a new acquisition of 120 images (duration 0.5 s each) was started. Finally, after further ingestion of 200 ml normal water, a series of 1-s images was taken for 2 min while the patient performed several Valsalva manoeuvres to induce reflux.

The persistence, rather than the intensity, of radioactivity in the gastric region was used for grading the reflux⁶. Four levels were identified. Grade 0 was the absence of reflux, minimal reflux lasting < 1 min, or that occurring in the first 10 min after injection. Grade 1 was repetitive reflux observed in the first 10 min after injection and grade 2, persistent reflux limited to the distal half of the stomach. Grade

3 reflux was persistent and involved the whole stomach up to the oesophagogastric anastomosis. Only grades 2 and 3 were considered abnormal.

The gastric emptying study was performed using a radiolabelled meal consisting of ^{99m}Tc -pertechnetate bonded to a polystyrene resin mixed with 100 ml hot whole milk, 2 g oatmeal and 3.5 g sugar⁷. This semisolid test meal contained simple carbohydrate (8.2 g), complex carbohydrate (17 g), animal protein (3.4 g), vegetable protein (5 g) and fats (5.4 g), and provided 745 J per portion. It is easy to prepare, and has the advantages that polystyrene resins are inert, non-toxic, minimally absorbable in the gastrointestinal mucosa, stable at gastric pH and capable of being uniformly mixed with solid food.

Anterior thoracic and upper abdominal images were obtained with the patient sitting erect in front of a wide-field γ camera equipped with a general-purpose, low-energy collimator and coupled to a computer. Data acquisition began immediately after ingestion of the meal, 1-min images being recorded for 1 h on a 64×64 matrix. Time-activity curves for gastric emptying were obtained using a gastric region of interest. The decay-corrected half-emptying time ($t_{1/2}$) was calculated, and values were compared with those obtained from a group of six healthy volunteer subjects. Gastric emptying studies were performed in 12 patients.

Manometry

A single-catheter assembly, consisting of four polyvinyl chloride tubes with four 2-mm lateral openings placed 5 cm apart at the distal end and radially oriented, was introduced nasally. The tubes were continuously perfused with distilled water at a rate of 0.8 ml/min by an Arndorfer pneumohydraulic pump (Arndorfer Medical, Greendale, Wisconsin, USA). Intraluminal pressures were transmitted through the water-filled catheter to external Statham transducers (Beckman 4-327C; Sensor Medics, Milan, Italy) connected to a polygraph.

The test was performed with the patient lying supine. A belt pneumograph was placed around the lower chest to record respiration. The manometric catheter was passed into the stomach and pulled back until the proximal side hole was located in the upper oesophageal sphincter and the two distal holes were in the intrathoracic stomach. The patient was asked to perform ten wet swallows of 5 ml water at 30-s intervals. The procedure was repeated after repositioning the catheter 5 cm distally to record pressure changes over the entire length of the stomach. Manometric studies were performed in seven patients; data were compared with those obtained from a group of 26 healthy volunteers.

Twenty-four-hour pH monitoring

Two glass pH probes (Ingold 440 M4; Urdorf, Switzerland) were introduced nasally and positioned 2 cm above the oesophagogastric anastomosis and in the middle portion of the intrathoracic stomach. The probes were calibrated in standard buffer solutions before and after monitoring. The correct position of the electrodes was checked using fluoroscopy. The probes were taped to the nose and connected to a portable solid-state recorder (Proxima 2; M&M, Bologna, Italy)

which sampled the pH every 8 s. The patients were asked to eat three standard meals, with the exclusion of food and drinks of extreme acidic or alkaline pH. Only water was permitted between meals. At the end of the test the position of the electrodes was again checked by fluoroscopy, and the probes were removed. The stored data were transferred to a personal computer (IBM PS2/30; IBM Italia, Bologna, Italy) and analysed by dedicated software (PC Light; M&M).

The gastric secretory profile was evaluated by analysing the area under the curve (AUC) at pH < 4 in the stomach. Acid exposure in the oesophagus was expressed as the percentage of total time at pH < 4, and alkaline exposure by the percentage of total time at pH > 7. The time during meals was excluded from analysis. Data obtained from patients were compared with those from 21 healthy volunteers, 11 men and ten women, whose ages ranged from 25 to 36 (median 31) years.

Statistical analysis

The AUC was calculated by the trapezoidal rule. The two-tailed Mann-Whitney *U* test was used to compare means. Statistical significance was accepted at $P < 0.05$.

Results

Eleven patients (69 per cent) had a positive DISIDA scan, that is grade 2 or 3 duodenogastric reflux (Figure 1). No association



Figure 1 Biliary excretion scintigraph showing grade 3 persistent duodenogastric reflux involving the entire intrathoracic stomach

Table 1 Endoscopic and scintigraphic findings in relation to symptoms in 16 patients

Patient no.	Symptoms	Endoscopy	Grade of duodenogastric reflux	Gastric emptying ($t_{1/2}$) (min)
1	—	Normal	0	33
2	Heartburn	Gastric ulcer	3	41
3	Heartburn	Gastritis	3	42
4	—	Gastritis	3	40
5	—	Gastric ulcer	2	—
6	Heartburn	Oesophagitis	0	20
7	Regurgitation	Gastritis	2	45
8	Heartburn	Oesophagitis	0	12
9	Dumping syndrome	Normal	2	5
10	Heartburn	Oesophagitis	3	—
11	Heartburn and regurgitation	Oesophagitis	2	22
12	—	Normal	1	—
13	—	Oesophagitis	2	—
14	—	Normal	0	8
15	Regurgitation and diarrhoea	Normal	3	30
16	Regurgitation	Normal	3	14

Table 2 Manometric measurements of intrathoracic stomach and proximal oesophagus in seven patients

Patient no.	Intragastric pressure (mmHg)	Upper oesophageal sphincter pressure (mmHg)	Upper oesophageal sphincter relaxation (%)	Amplitude of oesophageal waves (mmHg)
1	+15	68	100	40
3	+15	44	100	60
6	+12	62	100	40
7	0	45	100	38
8	+6	52	100	44
10	+22	66	100	45
12	+8	57	100	65

Table 3 Results of 24-h gastric and oesophageal pH monitoring

	Patients (n = 16)	Controls (n = 21)	P*
Stomach			
Area under curve (pH < 4)	96 818(59 715)	158 784(42 813)	<0.001
Percentage of total time at			
pH < 4	67.3(28.7)	88.9(8.9)	<0.001
pH 4-7	21.9(23.0)	9.9(7.3)	0.12
pH > 7	10.8(13.6)	1.2(3.2)	0.001
Oesophagus			
Percentage of total time at			
pH < 4	11.3(15.9)	3.0(2.1)	0.82
pH 4-7	77.1(20.8)	95.5(2.8)	<0.001
pH > 7	11.6(13.4)	1.5(2.5)	<0.001

Values are mean(s.d.). *Two-tailed Mann-Whitney U test

was found between the degree of reflux and the presence of symptoms. However, all five patients with endoscopic gastric lesions had pathological reflux, and two of them were asymptomatic (Table 1). There was no association between the degree of reflux or the presence of endoscopic lesions and the mean alcohol intake or the mean number of cigarettes per day.

The mean(s.d.) $t_{1/2}$ of the intrathoracic stomach was significantly lower in patients than in control subjects (26(14.3) versus 44(7.5) min, $P < 0.01$). The fastest emptying occurred in the patient with dumping syndrome (Table 1).

Manometry showed a positive resting pressure in the intrathoracic stomach. No propagated oesophageal waves or spontaneous motor gastric activity were recorded. In all patients mean(s.d.) upper oesophageal sphincter pressure was normal compared with that in control subjects (56.3(9.6) versus 46.6(14.6) mmHg, P not significant) and was presumably adequate to prevent the passage of oesophageal contents into the pharynx (Table 2).

The gastric AUC at pH < 4 was significantly less in patients than in controls, indicating that the intrathoracic stomach is still able to maintain an acidic intraluminal pH.

There was evidence of a greater gastric exposure to pH > 7 in patients, confirming the presence of duodenogastric reflux in these individuals. There was also a significantly greater oesophageal alkaline exposure in patients compared with control subjects (Table 3).

Discussion

The results of the present study show that bile reflux is a common finding in patients with a vagotomized intrathoracic stomach. This was confirmed by biliary excretion scintigraphic and pH studies. It has been speculated that pyloric denervation itself may reduce the barrier to reflux⁸. An additional factor inducing reflux may be the development of a pressure gradient between the gastric and duodenal lumen related to the negative

intrathoracic pressure and the positive intra-abdominal pressure^{9,10}. However, the resting intragastric pressure was positive in the patients studied. This is in agreement with the findings of other investigators¹¹ and is probably the result of vagotomy.

Another finding of this study is that the intrathoracic stomach, when compared with the normal stomach, has a significantly shorter emptying time in the upright position for a semisolid meal. This accelerated emptying may be due to loss of receptive relaxation and increased intragastric pressure after vagotomy, or to the influence of gravity on the stomach contents⁸. Both hypotheses are plausible, since it has been shown that the intrathoracic stomach does not actively contribute to the progression of the bolus but behaves like an inert conduit¹². The manometric studies performed in the present paper support this observation.

As a result of accelerated gastric emptying, one of the patients studied suffered from the dumping syndrome. Only three patients lost weight after surgery, confirming that major disturbances of food absorption are unusual after oesophagectomy and stomach replacement¹³.

It has been suggested that the intrathoracic stomach does not need a drainage procedure to facilitate emptying^{14,15}. We believe that a simple surgical manoeuvre, such as digital disruption of the pylorus, may prevent gastric outlet obstruction in the postoperative period¹⁶, and should not significantly increase the likelihood of bile reflux, a phenomenon that occurs even in the absence of pyloroplasty⁸.

Although gastric acid secretion is lessened by the truncal vagotomy performed during oesophageal resection, this does not result in achlorhydria. The technique of 24-h pH monitoring has been shown to be accurate and highly reproducible in validation studies comparing pH measurements with aspiration of gastric juice¹⁷. It appears from the data reported here that, at least 1 year after operation, the intrathoracic stomach is capable of producing acid, although less than in controls. Other investigators have found a striking decline in basal and maximal acid secretion and a rise in plasma gastrin levels after surgery¹⁸. However, hypergastrinaemia tends to settle, suggesting the possibility of restoration of the gastric secretory function after a period of quiescence¹⁹.

In the present study 24-h pH monitoring was also used to measure the oesophageal exposure to acid (pH < 4) and to alkaline (pH > 7) reflux. The threshold of pH 7 has been reported as a reliable indicator of oesophageal alkaline exposure²⁰. Simultaneous oesophageal and gastric pH monitoring in patients with reflux has shown that increases in intraoesophageal alkalinity to pH > 7 follow changes in gastric pH to the alkaline zone²¹. No statistical difference was found in the oesophageal acid exposure between patients and controls; this may be the result of reduced gastric acid secretion and mixing with alkaline duodenal refluxate in the patient population. Conversely, a significant increase in oesophageal alkaline exposure in patients was seen, which was associated with a positive DISIDA scan.

In addition, all patients with evidence of pathological

duodenogastric reflux on scintigraphy were found to have gastric mucosal lesions, whereas oesophagitis was also present in patients without duodenogastric reflux. Interestingly, the gastric AUC at pH < 4 was less in patients with than in those without reflux, indicating the buffering effect of the alkaline refluxate in the gastric environment.

It seems, therefore, that excessive duodenogastric reflux causes gastric mucosal damage and that acid reflux may be the primary cause of oesophagitis after oesophagogastrostomy. The relationship between buffer capacity and the injurious potential of the duodenal contents has not emerged from this study, and is still a matter of debate²².

In this study, three patients with pathological duodenogastric reflux on scintigraphy were asymptomatic despite the endoscopic presence of mucosal lesions. This is a not uncommon finding in clinical practice, having been shown in patients with recurrent peptic ulcer disease after medical²³ or surgical²⁴ treatment, and in patients with oesophagitis²⁵. Furthermore, the lack of association between the degree of reflux or the presence of endoscopic lesions and the daily alcohol and cigarette consumption seems to confirm that surgically induced duodenogastric reflux plays a major pathogenic role in these patients.

In agreement with the findings of other investigators²⁶, gastrointestinal function appears to recover well after oesophagogastrostomy, and most of the patients in the present study had resumed a near-normal diet 1 year after surgery. Although the performance status of patients was satisfactory, endoscopic lesions and symptoms related to reflux of gastroduodenal contents were frequent, indicating that long-term survivors after oesophagectomy and oesophagogastrostomy are at risk of complications related to the damaging action of acid and alkaline secretions.

Gastritis and gastric ulcer represent a common endoscopic finding⁸, whereas reflux oesophagitis seems to occur mostly in patients with a low intrathoracic anastomosis^{2,27}. Aspiration is an additional source of morbidity after oesophagogastrostomy¹ and respiratory complications represent the most frequent cause of death in those who survive for more than 5 years²⁸. This was not the case in the present study, and we agree with other investigators that an intact upper oesophageal sphincter, as demonstrated by manometry, is an important prerequisite for preventing oral regurgitation and aspiration²⁹.

It is concluded that, despite the potential complications, oesophagogastrostomy remains an excellent surgical procedure after oesophagectomy for cancer. Further studies are needed to investigate the pathophysiology of duodenogastro-oesophageal reflux, and to devise new therapeutic strategies for the prevention of mucosal damage.

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Thoracoscopic long oesophageal myotomy for nutcracker oesophagus: initial experience of a new surgical approach

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A thoracoscopic technique is described for the execution of long oesophageal myotomy for nutcracker oesophagus causing odynophagia and non-cardiac chest pain. The technique is based on a multipuncture method and a left thoracoscopic approach. It has been performed on three patients with complete symptomatic relief in the short term, although the follow-up period is short (maximum 12 months). No complications were encountered and discharge from hospital occurred by the fifth day after operation.

The current management of patients with non-cardiac chest pain is unsatisfactory. Such pain is generally associated with either reflux disease or motility disorders, e.g. symptomatic high-amplitude oesophageal peristalsis (nutcracker oesophagus), and less commonly with diffuse oesophageal spasm. Medical management includes antireflux medication and the use of nitrates, calcium antagonists and cimetopium bromide. Relief with these agents is uncertain and controlled studies have found them to be no better than placebo in relieving chest pain associated with diffuse oesophageal spasm and nutcracker oesophagus¹. Therapy with calcium channel blockers often precipitates or exacerbates existing gastro-oesophageal reflux. Only a small cohort of patients with intractable symptoms unresponsive to medical treatment or who require doses of these agents producing substantial side-effects is referred for surgical management. This involves long oesophageal myotomy tailored to the extent of the manometric abnormality, with or without an antireflux procedure. Although long oesophageal myotomy is effective in providing symptomatic relief in patients with diffuse oesophageal spasm and nutcracker oesophagus²⁻⁵, this procedure entails a posterolateral thoracotomy which is followed by a long convalescence. The thoracoscopic procedure described in this paper achieves this objective without resort to a thoracotomy.

Patients and methods

Patients

The patients were all women, aged 25, 42 and 38 years. They were referred because of non-cardiac angina-like pain unresponsive to medical therapy. In addition, one of the patients complained of pain on swallowing (odynophagia). Another gave a history of endoscopically confirmed duodenitis and was on maintenance treatment with ranitidine. The manometric features (Table 1) obtained by perfusion manometry using the standard Arndorfer system (Arndorfer Medical, Greendale, Wisconsin, USA) and a station pull-through technique were indicative of symptomatic high-amplitude oesophageal peristalsis (nutcracker oesophagus). There was no evidence of reflux in any of the three patients from 24-h ambulatory pH monitoring. Oesophageal transit measured by the radiolabelled solid-bolus egg-white test^{6,7} was prolonged in two patients (220 and 46 s) and normal in one (14 s).

Anaesthesia and patient position

General anaesthesia was carried out with a double-lumen endotracheal tube. The patient was placed in the left semiprone posterolateral thoracotomy position with the arm held well abducted to ensure maximum superior displacement of the scapula. The operating table was split to arch the left hemithorax and obtain maximal spread of the intercostal spaces.

Insertion of flexible endoscope

After induction of anaesthesia, a standard forward- or oblique-viewing flexible endoscope was introduced into the oesophagus and the tip

placed just below the oesophagogastric junction. Once in position, the light was switched off. This endoscope was subsequently used for two purposes: identification of the oesophagus in the aortovertebral gutter by transillumination, and endoscopic lifting of the organ to facilitate exposure and dissection.

Placement of cannulae

As shown in Figure 1, five cannulae were used. The inferior two were 11.5 mm in diameter, for use of the 10.0-mm 30° forward oblique telescope and insertion of a clip applicator and pledget swab for blunt dissection. The upper three cannulae, all 5.5 mm in diameter, were used for the insertion of grasping forceps, scissors and the electro-surgical hook-knife. Accurate placement of these access cannulae is critical for adequate exposure and ease of dissection. It is important that the posterior cannulae are placed anterior to the angle of the rib to avoid damage to the intercostal nerve which can produce distressing neuralgia after operation.

The first cannula to be inserted was the anterior upper 5.5 mm (fourth interspace). This was carried out under direct vision using a special technique that obviates the risk of damage to the lung parenchyma (Figure 2). The trocar-cannula assembly was introduced through a small stab incision in the intercostal muscle space. After removal of the trocar, the cannula was connected to the electronic insufflator set at minimum flow and a pressure of 6.0 mmHg. A 5.0-mm telescope attached to an endocamera was then introduced inside the cannula such that the tip of the optic lay just proximal to the oblique tip of the cannula, thereby visualizing the stretched tissues ahead of the latter device. The cannula was then carefully 'reamed' through the tissues by rotation with gentle force exerted from the wrist until the parietal pleura was breached, when the combined effect of the

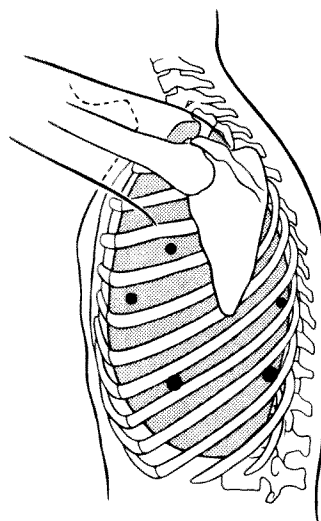


Figure 1 Position of placement of cannulae

Table 1 Manometric findings before operation

Patient no.	Wave amplitude (mmHg)			Wave velocity (cm/s)		Wave duration (s)			LOS pressure (mmHg)
	U	M	L	U	M	U	M	L	
1	53	137	215	1.8	5.8	3.3	5.3	8.3	13.0
2	142	177	171	4.0	4.0	4.2	4.0	4.9	23.8
3	107	180	227	6.8	4.2	4.4	4.5	4.6	23.0

U, upper oesophagus; M, middle oesophagus; L, lower oesophagus; LOS, lower oesophageal sphincter

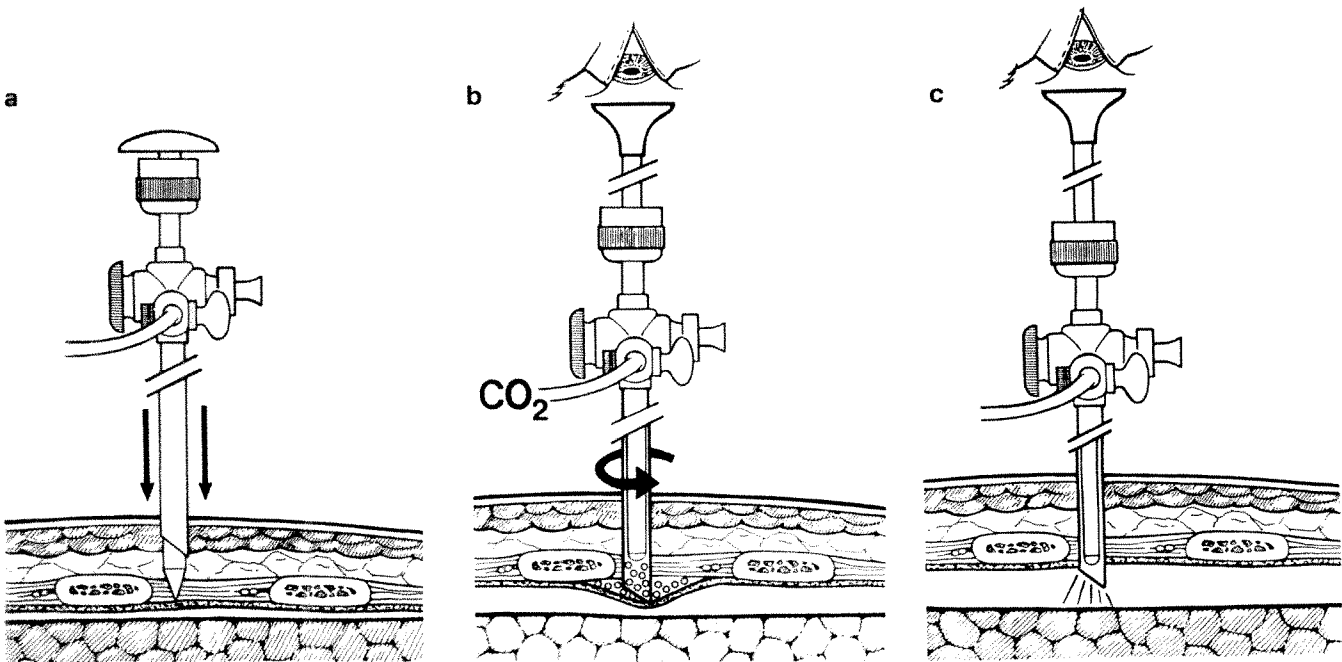


Figure 2 Technique of insertion of the initial 5.5-mm cannula to avoid damage to the lung parenchyma. **a** Insertion of trocar-cannula to intercostal muscle layer; **b** removal of trocar and insertion of 5-mm telescope; rotation advancement of bevelled cannula ahead of optic; **c** penetration of parietal pleura by tip of bevelled cannula

insufflating carbon dioxide flow pressure and lung compliance resulted in collapse of the underlying lung away from the cannula tip. The remaining cannulae were then inserted under direct vision after their optimal position had been ascertained from within by the indentation of the relevant intercostal space.

Intrathoracic pressure and cardiac monitoring

The safety of the procedure was dependent on the avoidance of mediastinal shift which may occur rapidly and lead to hypotension and cardiac arrhythmia if the pressure within the hemithorax exceeds 8.0 mmHg. A working pressure of 6.0 mmHg (preselected on the electronic insufflator) has been observed to provide this safety margin and ensure satisfactory lung collapse.

Essential cardiovascular monitoring included: electrocardiography, central venous pressure, arterial pressure and urine output. A Swan-Ganz catheter for monitoring of the pulmonary wedge pressure and cardiac output is used only in patients with established heart disease.

Operative details

The first landmark to be identified was the inferior pulmonary ligament. This was divided with scissors using electrocautery to small vessels crossing this membrane. The identification of the lower oesophagus was then readily achieved by switching the light source of the flexible endoscope and dimming the light to the thoracoscope endocamera assembly.

The mediastinal pleura over the hiatal margin was divided. Several small vessels required control by electrocoagulation during this step. It was important that a dry field was kept as even minor oozing results in pooling of blood in the aortovertebral gutter, with impairment of vision. The dissection of the anterior surface of the lower oesophagus

was considerably facilitated by flexing the tip of the endoscope forwards, thereby lifting the organ from its gutter (Figure 3). Complete mobilization of the entire circumference was unnecessary, the dissection being limited to exposure of the anterior half of the circumference of the oesophagus. The mobilization of the lower oesophagus was completed when the phreno-oesophageal membrane and its attachment to the oesophagogastric junction had been exposed. At this stage the vagal trunks were identified and preserved.

The dissection then proceeded in a cephalad direction with division of the mediastinal pleura medial and parallel to the descending thoracic aorta until the lower limit of the aortic arch was reached (Figure 3). The inferior pulmonary vein must be gently mobilized from the oesophagus and retracted medially with the lung parenchyma.

Once the mediastinal pleura had been divided, further mobilization of the left lateral half of the circumference of the oesophagus was needed. For this purpose, lifting of the oesophagus from the gutter was achieved by traction on the grasped medial and lateral edges of the cut mediastinal pleura. This was aided, when necessary, by forward flexion of the flexible endoscope. This stage of the oesophageal mobilization was carried out with a mixture of scissors and pledget swab dissection. A constant direct aortic branch to the oesophagus was encountered just above the inferior pulmonary vein. This vessel was secured by clipping before division.

The myotomy was commenced in the lower oesophagus. At this stage it was considered safer to resort to monocular vision directly through the telescope. For this reason an image-corrected beam splitter (Karl Storz, Tuttlingen, Germany) was inserted between the telescope and the endocamera. This allowed simultaneous direct viewing by the surgeon and television monitoring for the assistant and nurse. There was no doubt that both resolution and depth perception were incomparably better on direct viewing. This approach was needed to

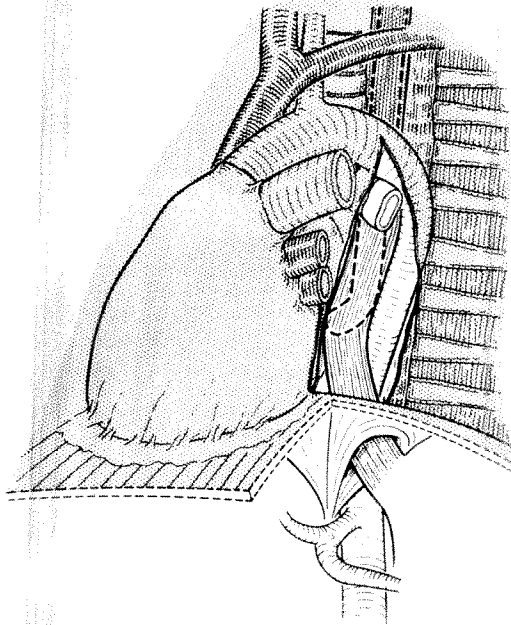


Figure 3 Use of the flexible endoscope to lift the gullet out of the aortovertebral gutter. Division of the mediastinal pleura was carried out medial and parallel to the aorta and extended from the hiatus to the aortic arch

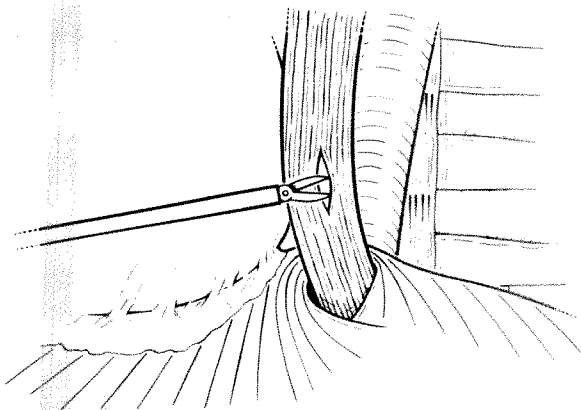


Figure 4 The myotomy was started at the lower end using the twin-action scissors to separate the muscle fibres until the submucosal plane was exposed

perform the procedure with safety in terms of avoidance of perforation of the oesophageal mucosal tube during the myotomy.

The myotomy was started using twin-action scissors (Karl Storz) until the submucosal plane was reached. This was then opened by distraction of the scissor blades (Figure 4). The submucosal plane was then separated from the muscle layers using blunt (closed) scissor dissection. The L shaped electrosurgical hook was then introduced and used to lift, stretch and tent the muscles away from the mucosal tube before blender current was applied. The tenting of the muscle layers away from the mucosal tube was crucial. Furthermore, the resulting compression of the stretched muscle fibres by the hook altered their electrical conductivity and thus localized the coagulation process to the cut area (Figure 5). The myotomy was extended in a cephalad direction until the aortic arch was reached. Nerves which crossed the line of the myotomy were mobilized and lifted up such that the myotomy could proceed without their division.

If the lower oesophageal sphincter was normal it was left intact. If hypertensive, the myotomy was extended to the gastro-oesophageal junction. This was more difficult because of the inadequate submucosal plane as the stomach was reached, but with care and direct monocular vision this step could also be executed without mishap. The myotomy was not extended across the cardio-oesophageal junction to the stomach.

At the end of the procedure, the endoscope was withdrawn from the oesophagus and replaced by a nasogastric tube. The hemithorax was irrigated with warm isotonic saline to clean the aortovertebral gutter. A chest drain was inserted through one of the access cannulae

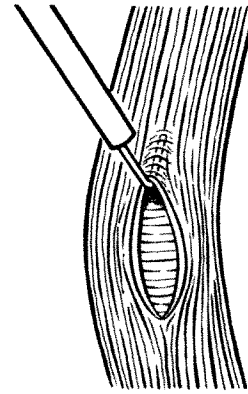


Figure 5 The L shaped electrosurgical hook was used to lift, stretch and tent the muscles away from the mucosal tube before blender current was applied. As the electrical conductivity of the muscle layers was altered at the point of compression-lift by the hook, the coagulation process was limited to the cut area

and the lung inflated. The stab wounds were infiltrated with bupivacaine and edges approximated with subcuticular polyglactin. The duration of the three operations was 3 h, 2 h and 1 h 30 min. No measurable blood loss was encountered in any patient.

Results

Postoperative course

As with other experience of thoracoscopic surgery in this department⁸, lung reinflation after operation was rapid and uncomplicated in all three patients, although one developed a minor chest infection. There were no other infectious complications. The nasogastric tube was removed within 24 h of operation and oral feeding started on the second day after chest radiography had confirmed the absence of air or fluid leak. Pain was minimal, consisting of chest soreness during the first 12 h. All three patients were fully ambulant by the first day after operation and were discharged on day 4 (two patients) or day 5.

Clinical follow-up

The follow-up was short (maximum 12 months) but to date symptomatic review has confirmed complete relief of non-cardiac chest pain and dysphagia. One patient, a smoker, has developed epigastric pain and is undergoing investigation for possible duodenal ulceration. She has a history of endoscopically proven duodenitis and has been receiving ranitidine therapy. Manometric studies to date have shown very low amplitude contractions or aperistalsis.

Discussion

The current controversies relating to the pathogenesis, diagnosis and treatment of oesophageal chest pain have been reviewed recently⁹. The most common motility disorder in these patients is the nutcracker oesophagus which is found in 27–48 per cent of cases¹⁰. The exact mechanism responsible for the pain remains unknown, although the findings of a recent study on the capacity of the oesophageal blood flow to rewarm the oesophagus after a cold challenge are suggestive of ischaemia, resulting from the high-amplitude contractions or spasm¹¹.

A collective review of long oesophageal myotomy, involving 199 operations from ten reports between 1964 and 1982, showed that this procedure resulted in symptomatic relief in 77 per cent of patients suffering from hypermotility disorders². None the less, this operation is infrequently performed for symptomatic hypermotility disorders despite the generally acknowledged view that medical therapy is unsatisfactory in a substantial cohort of patients, certainly far in excess of the 5 per cent who are treated surgically⁵. The reason for this reluctance to resort

to surgical management probably stems from the need for an extensive thoracotomy. There is no doubt, aside from the morbidity and prolonged convalescence, that thoracotomy is frequently accompanied by intractable chest pain, including neuralgia which is difficult to treat and often requires referral to a specialist pain clinic. Restricted shoulder movement due to scapular fixation and a frozen shoulder joint are also common after thoracotomy and account for a significant disability and reduced capacity for work.

This initial experience with the thoracoscopic approach has shown that a long myotomy tailored to the abnormality (distal two-thirds with sparing of the lower oesophageal sphincter) can be achieved with safety; there is good symptomatic relief with rapid recovery, early discharge and accelerated convalescence. The thoracoscopic myotomy performed on these patients was not accompanied by an antireflux procedure as the endoscopic procedure does not disturb the normal anatomy of the lower oesophagus. However, longer follow-up is needed to determine whether reflux with defective clearance is induced by tailored thoracoscopic myotomy.

Addendum

Since submission of this report, a further six patients with non-cardiac chest pain and motility disorders have been treated with thoracoscopic long myotomy at this hospital. To date, relief of pain has been obtained in eight of nine patients.

Acknowledgements

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Management of empyema thoracis at Lusaka, Zambia

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Of the 39 consecutive patients with empyema thoracis managed by one of the five general surgical units at Lusaka, Zambia, 26 suffered from human immunodeficiency virus (HIV) infection and 19 were diagnosed as suffering from pulmonary tuberculosis within 3 years of developing empyema thoracis. Thirty patients were between 16 and 40 years of age; of these, 22 suffered from acquired immune deficiency syndrome (AIDS) and all 19 patients with pulmonary tuberculosis belonged to this age group. Of the four patients with empyema thoracis in the age group of 0-5 years, two were suffering from AIDS. The majority of cases of empyema thoracis associated with AIDS present insidiously and, because of late presentation, rib resection is necessary. After surgery these patients were managed at home with the help of a home care team, thus reducing the burden on hospital resources. The morbidity and mortality rates in these patients are higher than in those in whom empyema thoracis is not associated with AIDS.

Recently the consensus of opinion of clinicians is that the incidence of empyema thoracis and tuberculosis is on the increase in the University Teaching Hospital, Lusaka¹. This might be explained partly by population increase in third world countries and urbanization. It is well known that human immunodeficiency virus (HIV) infection has a strong association with pulmonary disease, particularly tuberculosis, and so it is obvious that empyema thoracis will be associated with high rates of HIV seropositivity. Elliot *et al.*¹ reported an HIV seropositivity rate of 49 per cent in Zambian patients with confirmed pulmonary tuberculosis and 81 per cent in those with pleural diseases. This study was undertaken to find out how best to manage empyema thoracis in this situation. Patients with empyema thoracis and acquired immune deficiency syndrome (AIDS) occupy hospital beds for prolonged periods and are a major burden on hospital resources. Early discharge and home care would lessen the burden.

Patients and methods

This cross-sectional study was carried out between 1 April 1989 and 30 March 1990 in one of the five general surgical units of the University Teaching Hospital, Lusaka. The institution is both a provincial and a referral centre which caters for the western, central, southern and eastern parts of the country; patients either present directly or are referred from peripheral hospitals. Patients with confirmed tuberculosis are notified and kept under review at the chest clinic. Of 39 patients with empyema thoracis, eight came directly under our care and 24 presented to medical units and were subsequently referred to us for surgical management. A further seven patients who were under review at the chest clinic developed empyema thoracis and were referred to the unit.

Serological testing for HIV-1 was carried out using an enzyme-linked immunosorbent assay (ELISA) technique (Recomigen HIV-EIA; Cambridge Bioscience, Worcester, Massachusetts, USA), the sera being tested in duplicate. All positive tests were checked by another ELISA technique (Abbott-Abbott Laboratories, North Chicago, Illinois, USA). Because of financial constraints Western blot testing was not available for this study. There were two patients with pulmonary tuberculosis who were seronegative and their serological status was also tested by Wellcozyme Recombinat (Wellcome Diagnostics, Dartford, Kent); these two patients were considered not to have HIV infection. Infection with HIV-2 is negligible in Zambia.

Once empyema thoracis had been diagnosed, the chest was aspirated with a 21 Fr needle and the rate of flow of pus into a 10-ml syringe was noted as 'easy' or 'difficult'. Easy flow was defined as filling of the syringe by one pull on the plunger. The flow was defined as difficult if two or more pulls were required.

All patients with empyema thoracis underwent intercostal underwater seal drainage for 2 weeks from the most dependent part

(determined radiographically). The lumen of the tube was 1 cm in diameter and the length of the tube in the chest about 7.5 cm. If drainage persisted at the end of 2 weeks, 7.5-cm long parts of two ribs were resected at the site of intubation. Patients with open drainage were encouraged to sit in a bath daily and were instructed to flush the cavity with water, blow in surgical gloves and sleep on the side of drainage. Two patients with empyema necessitatis were treated with adequate incision and drainage. Three patients with encysted empyema thoracis associated with lung abscesses were treated expectantly because of the possibility of creating a bronchopleural fistula.

In 19 patients who were diagnosed as suffering from pulmonary tuberculosis within 3 years of developing empyema thoracis, the empyema was presumed to be tuberculous; 12 of these patients did not comply with antituberculosis chemotherapy and seven developed empyema thoracis while under treatment at the chest clinic. All patients with a history of tuberculosis and those who were seropositive for HIV were started on antituberculosis chemotherapy. None of the patients had previously received blood or blood products and none was an intravenous drug abuser.

Results

Thirty-nine consecutive patients with empyema thoracis were studied; 33 male and six female. Of these, 26 were seropositive for HIV (23 male and three female) and suffered from AIDS as defined by the World Health Organization². A seropositive patient was considered as suffering from AIDS if he or she had three or more of the following: generalized lymphadenopathy, marked loss of weight, prolonged unexplained fever, oral thrush, chronic unexplained diarrhoea, pulmonary tuberculosis and typical mucocutaneous lesions. This hospital lacks the facilities to use the Walter Reed system of staging the disease.

Nineteen patients were diagnosed as suffering from pulmonary tuberculosis (17 male and two female) on radiography and/or sputum examination within 3 years of developing empyema thoracis. Of this 19, 12 had not complied with full antituberculosis chemotherapy and seven were under review at the chest clinic.

Two patients who had confirmed pulmonary tuberculosis were seronegative for HIV; the rest suffered from AIDS. Table 1 shows the mode of presentation and Table 2 the duration of symptoms of empyema thoracis. Table 3 shows the age distribution of patients who suffered from pulmonary tuberculosis and AIDS, and Table 4 shows both the surgical procedures carried out for empyema thoracis in patients who suffered from AIDS, and the mean hospital stay.

In the 0-5-years age group two HIV-negative patients developed empyema thoracis following bronchopneumonia complicating measles. The other two patients with AIDS

Table 1 Mode of presentation of 39 patients

Presentation	No. of patients
Cough	30
Chest pain	29
Generalized lymphadenopathy	28
Weight loss	11
Oral thrush	11
Fever	10
Breathlessness	6
Diarrhoea	3
Haemoptysis	2
Body pains	2
Empyema necessitatis	2

Table 2 Duration of symptoms in 39 patients

	No. of patients	Mean (range) duration (days)
HIV-negative	13	5 (2-14)
HIV-positive	26	60 (14-150)

HIV, human immunodeficiency virus

Table 3 Ages of 39 patients with empyema thoracis, and incidence of AIDS and pulmonary tuberculosis

Age (years)	No. of patients with empyema thoracis	No. of patients with AIDS	No. of patients with pulmonary tuberculosis
0-5	4	2	0
6-15	1	0	0
16-40	30	22	19
41-60	3	2	0
61-80	1	0	0

AIDS, acquired immune deficiency syndrome

Table 4 Surgical procedure and length of hospital stay

Procedure	No. of patients	No. of patients with AIDS	Mean hospital stay (days)
Intercostal drainage only	22	9	10
Rib resection after 2 weeks of intercostal drainage	12	12	8*
Expectant (encysted empyema with lung abscesses)	3	3	21
Incision and drainage (empyema necessitatis)	2	2	14

AIDS, acquired immune deficiency syndrome. *Time after rib resection; patient allowed home with discharging sinus

presented with empyema necessitatis. Their HIV infection was presumed to have been contracted *in utero*. One of the mothers refused to be tested for HIV and the other was not available. Neither child had received blood or blood products before hospital admission. In the 61-80-years age group, the single case of empyema thoracis was secondary to pneumonia complicating femoral fracture.

In the group which underwent intercostal drainage alone, eight of the nine patients with AIDS had easy aspiration; 13 HIV-negative patients also had easy aspiration. All patients in the other groups (Table 4) had difficult aspiration. Of the 26 patients with AIDS, three died within 2 weeks of their first admission.

Seventeen patients with AIDS attended for follow-up at

intervals varying from 8 weeks to 8 months. Of these, five were readmitted within 6 (mean 4) months and died in hospital. Of the 17 patients, eight had dried up sinuses and nine intermittent discharge. All patients with HIV-negative status did well, with good lung expansion and resolution of wounds.

Discussion

The prevalence of seropositivity for HIV-1 in the hospital population in Lusaka is about 24 per cent, and is 10 per cent in blood donors^{3,4}. This rises to 60 per cent in patients suffering from tuberculosis in general and to 49 per cent in those with pulmonary tuberculosis^{1,4}. Present findings confirm other reports that AIDS associated with pulmonary tuberculosis predominantly affects young productive males in this environment. The World Health Organization survey carried out in Lusaka in 1990 noted that the incidence of tuberculosis had doubled since 1986. AIDS is characterized by activation of other latent infections acquired in early life⁵, and in an environment such as ours latent infection with tuberculosis is present in most adults⁶.

The mean duration of symptoms of 2 months in patients with AIDS suggests that development of empyema thoracis is an insidious process with chronic cough, chest pain and generalized lymphadenopathy as main complaints. Only a quarter of patients give a history of fever. By the time these patients come to surgeons, the aspirate is thick and 'difficult'. It is generally agreed by thoracic surgeons that open drainage by rib resection is the drainage procedure of choice when pus has one-third as sediment. A decision can be made about management, either by intercostal underwater seal drainage or by open drainage by rib resection, at the time of diagnostic thoracentesis, based on the technique of aspiration described. In this study all except one patient with difficult aspirate needed open drainage. It is now the policy of this unit to resect ribs without initial underwater seal drainage in patients with difficult aspirate; no adverse effects of this policy such as lung collapse or mediastinal shift have been encountered. There were no deaths after rib resection in patients with AIDS. About 50 per cent of these patients had dried up sinuses at 8 weeks; the others had intermittent discharge which was easily managed by the home care team, thus reducing the burden on hospital resources. The mean stay of patients after rib resection was 8 days. For cases of entrapped collection the sinus could be excised and drainage re-established under local anaesthesia. Recently this procedure has been carried out and patients have been allowed home on the second day.

Empyema thoracis associated with HIV in well established cases of AIDS carries an expectedly high mortality rate. In this study, on the other hand, all patients with empyema not associated with HIV infection did well. Of those with AIDS three never left hospital and of 17 who were followed up five died within 6 months.

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Early gastric cancer

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Early gastric cancer comprises more than 30 per cent of gastric carcinomas treated in Japan but remains an uncommon entity in the western hemisphere. A retrospective review of 48 patients with early gastric cancer undergoing operative treatment between 1965 and 1984 was carried out. The mean patient age was 70 years, in 31 men and 17 women. Preoperative diagnosis was made in 88 per cent of patients undergoing oesophagogastrroduodenoscopy with biopsy but upper gastrointestinal radiography was diagnostic in only 20 per cent. Surgical management consisted of subtotal gastrectomy (86 per cent), total gastrectomy (10 per cent) and wide local excision (4 per cent). The operative mortality and morbidity rates were 0 and 38 per cent, respectively. Mean follow-up was 7.7 years, with 44 per cent of patients still alive. Multivariate analysis disclosed only a healthy Eastern Cooperative Oncology Group score ($P = 0.002$) and a diploid DNA tumour pattern ($P = 0.05$) as significant prognostic variables of survival. The overall survival rate of patients with early gastric cancer (70 per cent at 5 years) was equivalent to that of an age- and sex-matched control population.

Over the past five decades the incidence of gastric cancer in the USA has declined steadily to approximately 24 000 new cases per year¹. Despite advances in diagnosis and therapeutic treatment, the overall 5-year survival rate of 15 per cent has remained constant. In those with gastric cancer, there is a subset of patients with early gastric cancer who have an excellent prognosis (nearly 100 per cent 5-year survival). Early gastric cancer, as defined in 1962 by the Japanese Society of Gastroenterological Endoscopy, is a gastric adenocarcinoma confined to the mucosa or submucosa irrespective of lymph node involvement.

Although common in Japan and the focus of intense study, early gastric cancer remains a rare entity in the USA. Few reports from the western hemisphere have appeared since the earliest clinical review of superficial spreading gastric cancer (pathologically the same entity as early gastric cancer) published in 1962². The present study determined the incidence, clinical presentation, treatment and outcome of patients with early gastric cancer and compared findings with those of other published reports.

Patients and methods

From 1965 to 1984 the Mayo Clinic tumour registry recorded 2397 operative resections for gastric cancer. Review of all pathological reports identified 71 patients with the diagnosis of early gastric cancer. All available specimens (64) were re-examined by the study pathologist (H.A.C.) and 48 patients were confirmed to have gastric adenocarcinoma confined to the mucosa or submucosa. Sixteen patients were excluded after review because of the absence of carcinoma in 14 instances (benign mucosal biopsy, four; dysplasia, four; benign adenoma, three; benign gastric ulcer, two; Barrett's oesophagus, one), one advanced gastric carcinoma, and one gastric lymphoma. Specimens were evaluated for histological grade (Broders³) and Laurén classification⁴. The DNA content of paraffin-embedded tissue was measured by flow cytometry using the method of Gonchoroff *et al.*⁵. Performance status was estimated by the criteria of the Eastern Cooperative Oncology Group (ECOG)⁶: 0 is asymptomatic; 1 is symptomatic, fully ambulatory; 2 is symptomatic, in bed for less than half of the day; 3 is symptomatic, in bed for more than half of the day but not bedridden; and 4 is bedridden.

Patient histories were reviewed to document the clinical presentation, diagnostic evaluation, operative therapy and post-operative course. Patient status was determined by follow-up examination or telephone contact. Analysis of discrete and continuous variables was performed using the log rank test⁷ and Cox's proportional

hazards model⁸. Estimates of survival for the study group and an age- and sex-matched control population (1970 North Central USA) were compared using the method of Kaplan and Meier⁹. Multivariate associations of survival were investigated using the model of Cox⁸.

Results

Presentation

There were 31 men and 17 women in the study population with a mean age of 70 (range 47-84) years. All patients were symptomatic on presentation. The physical signs and symptoms included epigastric pain (30 patients), anorexia and weight loss (19), nausea (19), melaena (12), vomiting (eight), fatigue (eight), dysphagia (four) and fever (two).

Diagnostic evaluation

A variety of diagnostic procedures was used over the study period. Forty patients underwent contrast examinations (barium upper gastrointestinal radiography) or oesophagogastrroduodenoscopy with biopsy (Table 1). Eight patients with persistent symptoms of dyspepsia, despite medical therapy, underwent laparotomy without either evaluation. Of 22 patients undergoing both procedures, endoscopy with biopsy was diagnostic in 19 while only six barium studies were diagnostic ($P < 0.01$) (Table 1).

Operative treatment

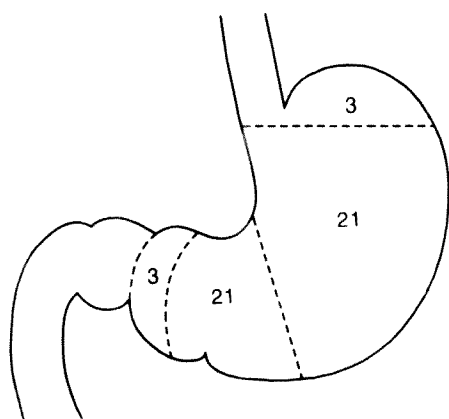
Operative management varied from wide local excision in two elderly women to total gastrectomy in five patients with proximally located neoplasms. The types of gastric resection and anastomotic reconstruction are summarized in Table 2. The

Table 1 Preoperative evaluation of 48 patients with early gastric cancer

Interpretation	Upper gastrointestinal radiography	Oesophagogastrroduodenoscopy and biopsy
Diagnostic	6	28
Suspicious	10	4
Benign	12	0
Negative	2	0
Total	30	32

Table 2 Operative management of 48 patients with early gastric cancer

	n	No. of 5-year survivors
Gastric resection		
Wide local excision	2	1
Subtotal gastrectomy	30	21
Radical subtotal gastrectomy	11	7
Total gastrectomy	5	4
Reconstruction		
Gastrotomy	2	1
Billroth I	17	10
Billroth II	18	15
Oesophagojejunostomy	5	4
Other	6	3

**Figure 1** Location of early gastric cancer in 48 patients. The majority of tumours were located in the gastric antrum and body

mean(s.d.) proximal margin of resection was 5.5(3.2) cm, and that of the distal margin 5.1(3.1) cm. No synchronous non-gastric neoplasms were discovered at the time of abdominal exploration.

Pathology

The majority of early gastric cancers were confined to the body and antrum (Figure 1). Tumour size ranged from 0.3 to 8.0 cm in greatest dimension (mean(s.d.) 3.0(2.0) cm). The depth of invasion was limited to the mucosa in 22 patients and involved the submucosa in 26. Seven patients had perigastric (N1) metastatic lymph node involvement. All regional (N2) lymph nodes included with the tumour specimen were free of metastatic involvement. Using the Laurén classification, more than half of the tumours were of the intestinal type (Table 3). Tumours were divided by histological grade as follows: I, ten; II, six; III, 11; IV, 21. The DNA content of early gastric cancer tumours was diploid in 23, tetraploid in six, aneuploid in 13, and indeterminate in six cases.

Complications

Patients were hospitalized for a mean of 14.3 (range 9–36) days. No 30-day operative deaths occurred but one patient died while hospitalized secondary to aspiration pneumonia. Two patients required reoperation, one for gastric haemorrhage and a second because of an anastomotic leak (oesophagojejunostomy). Fourteen infectious complications were identified (ten respiratory, three wound and one urinary tract). Partial small bowel obstructions in two patients resolved with non-operative therapy.

Patient outcome

The mean follow-up of all patients was 7.7 (range 4–24) years. Twenty-one patients remain alive, one with recurrent

carcinoma. Three patients have died from metastatic tumour progression. The remaining 24 patients died from causes unrelated to their gastric cancer. Tumour recurrence occurred in four women with pathologically diverse carcinomas (Table 4). Biopsy-proven pulmonary metastases were documented in two patients 5 years after resection. The remaining two women died 4 years after resection from biopsy-proven intra-abdominal carcinomatosis.

Patient survival at 5 and 10 years was equivalent to that of an age- and sex-matched population (Figure 2). The disease-specific survival rate was 92 per cent at both 5 and 10

Table 3 Univariate analysis of clinical and pathological factors correlating with survival in 48 patients with early gastric cancer

	<i>n</i>	5-year survival rate (%)	<i>P</i> †
Clinical factors			
Age (years)			
≥ 68	23	61*	} 0.0002
< 68	25	76	
Sex ratio (M:F)	31:17	71:65	0.25
ECOG score			
0	10	100	} 0.0012
1	20	70	
2	13	53	
3	5	40	
Blood group			
A	21	66	} 0.62
O	18	72	
AB	1	0	
B	8	75	
Weight loss before operation (> 5 lb (2.3 kg))			
Yes	29	66	} 0.17
No	19	74	
Abdominal pain before operation			
Yes	30	70	} 0.52
No	18	66	
Gastrointestinal haemorrhage before operation			
Yes	14	71	} 0.47
No	34	67	
Pathological factors			
Tumour location			
Antrum	21	76	} 0.16
Body	21	57	
Cardia	1	0	
Gastro-oesophageal junction	2	50	
Pylorus	3	100	
Histological grade			
I/II	16	56	} 0.18
III, IV	32	75	
Depth of invasion			
Mucosa	21	71	} 0.24
Submucosa	27	67	
Lauren classification			
Diffuse	19	79	} 0.47
Intestinal	27	63	
Mixed	2	50	
Nodal involvement			
Yes	7	71	} 0.77
No	41	68	
DNA ploidy status			
Diploid	23	82	} 0.05
Tetraploid	6	67	
Aneuploid	13	54	
Indeterminate	6	50	

ECOG, Eastern Cooperative Oncology Group. *Expected 5-year survival rate for healthy age- and sex-matched controls: age ≥68 years, 64 per cent; age <68 years, 88 per cent (gives an age-adjusted *P* value of 0.21). †Log rank test

Table 4 Early gastric cancer recurrences

Patient no.	Age (years)	Sex	Tumour characteristics							Site of recurrence
			Gross appearance	Size (cm)*	Depth of invasion	Lymph node involvement	Laurén classification	Grade†	Ploidy	
1	76	F	Polypoid	7.0	Mucosa	No	Intestinal	I	Diploid	Lung
2	54	F	Ulcerated	2.5	Mucosa	No	Diffuse	IV	Diploid	Abdomen
3	59	F	Polypoid	6.0	Submucosa	No	Diffuse	I	Tetraploid	Abdomen
4	49	F	Ulcerated	2.0	Submucosa	Yes	Intestinal	IV	Diploid	Lung

*Largest dimension; †histological grade using Broders' criteria

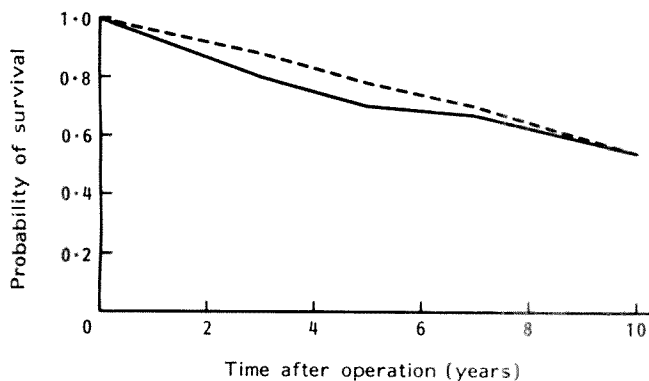


Figure 2 Survival curves for patients with early gastric cancer undergoing surgical resection (—) and age-matched controls (---) ($P = 0.41$ after 5 years, log rank test)

years of follow-up. Univariate analysis revealed a significant survival advantage for patients aged less than 68 years, an ECOG performance status of 0 or 1, and a tumour with diploid or tetraploid DNA pattern (Table 3). Multivariate analysis disclosed a survival advantage for patients with an ECOG score of 0 or 1 ($P = 0.002$) and patients with diploid tumours ($P = 0.05$).

Discussion

The demographics of this study were similar to those of previously published reports. The only significant prognostic factors for survival were an ECOG score of 0 or 1 and a diploid DNA tumour pattern. The overall survival rate of patients with early gastric cancer undergoing gastric resection was equivalent to that of healthy age- and sex-matched controls.

The prevalence of early gastric cancer in men exceeded that in women by nearly 2:1, a finding consistent with other reports^{10–14}. In contrast to previously published work, the patients in this series were older, with a mean age of 70 years. Representative data from the UK¹⁵, Brazil¹⁶, Japan¹⁷ and Spain¹⁸ had mean patient ages of 62.3, 60.0, 57.0 and 54.8 years, respectively. This age difference may result from a tertiary referral pattern. Other investigators from the USA^{10,11} have noted mean patient ages ranging from 44.0 to 69.0 years.

Endoscopy with biopsy was more sensitive and more specific than upper gastrointestinal radiography. Nearly half of the radiological studies were 'negative' or 'benign' in patients later found to have early gastric cancer. The mean delay to diagnosis after upper gastrointestinal evaluation was 3 months. Most of the false-negative upper gastrointestinal studies were performed before routine use of endoscopy. With double-contrast techniques, the radiological sensitivity has improved¹⁹ but it remains less sensitive than oesophagoduodenoscopy for early gastric cancer. There was no benefit in differentiating between early and advanced gastric cancer or benign and malignant disease in those patients undergoing abdominal computed tomography before operation. None of the 48 patients underwent endoscopic ultrasonography to delineate tumour depth²⁰.

Operative management varied because of patient age, comorbid conditions and tumour characteristics, but a subtotal gastrectomy with Billroth I or II reconstruction was preferred. No long-term survival advantage was detected for any type of gastric resection or anastomotic reconstruction. In larger Japanese studies of patients with advanced and early gastric cancer, survival benefit occurs after radical gastrectomy and extended lymphadenectomy^{21,22}. Given the low incidence of early gastric cancer in the western hemisphere and the less extensive lymphadenectomy routinely performed, these findings cannot be confirmed.

Patients with distal early gastric cancer have an improved prognosis compared with those with proximal tumours^{18,23}. While not statistically significant, the 10-year survival rate for patients with pyloric (100 per cent) and antral (61 per cent) early gastric cancer was better than for those with tumours of the gastric corpus (36 per cent) and proximal stomach (33 per cent). This survival advantage may stem from an earlier presentation of patients with distal gastric tumours.

The Laurén classification has been an unreliable predictor of patient survival^{18,24,25}; this study confirms this finding. Tumour grade, depth of tumour invasion and the presence of nodal involvement did not correlate with patient outcome. The more extensive Japanese experience with early gastric cancer demonstrates a slight, but significant, survival advantage for patients with mucosal early gastric cancer without nodal metastases²⁶. Ichiyoshi *et al.*²⁷ reported an increased risk of tumour recurrence with deeper tumour penetration (submucosal greater than mucosal).

de Aretxabala *et al.*²⁸ showed improved survival among patients with diploid early gastric cancer and patients with greater than 10 per cent polyploid cells ($\geq 3N$) fared poorly (5-year survival rate 36.3 per cent). This survival advantage may relate to nearly all mucosal early gastric cancers being diploid, a finding described by others^{29,30}. Improved survival occurs in patients with diploid tumours, but it is unclear whether this advantage is the result of other concurrent factors or independent of other variables.

A greater incidence of synchronous and metachronous non-gastric malignancies has been reported for patients with early gastric cancer. Green *et al.*¹⁴ found that nearly one-third of patients subsequently developed cancers at other sites. Eight of 109 patients of Itoh *et al.* died from a non-gastric malignancy¹⁷. In this study, cardiovascular disease was the most common cause of death and second primary tumours were not noted. Four patients developed recurrence of gastric cancer and three died from metastatic disease.

Early gastric cancer was found in only 2 per cent of 2397 patients undergoing gastric resection for cancer during a 20-year period. The reasons for this are the stringent histological criteria for early gastric cancer, the nature of surgical practice in the USA and the common failure to diagnose gastric cancer at an early stage. Bringaze *et al.*¹⁰, Oleagoitia *et al.*¹⁸ and Ohta *et al.*³¹ have documented higher prevalences of early gastric cancer among patients with gastric carcinoma, ranging from 5 to 33 per cent. The aggressive screening measures adopted in Japan have resulted in a marked increase in the prevalence of early gastric cancer. Some Japanese institutions have reported greater than 50 per cent of all gastric cancers as early³². Although

earlier evaluation of dyspeptic patients might increase the detection of early gastric carcinoma, the low incidence of this cancer in western countries makes mass screening economically impractical^{10,18}.

The crude 5- and 10-year survival rates of 70 and 58 per cent were substantially lower than the 90–95 per cent survival rates reported for Japanese patients^{17,22,26,31}. This may be a factor of patient age, since the survival in patients with early gastric cancer was equivalent to an age- and sex-matched control population. Green *et al.* have shown that the survival rate of patients with early gastric cancer is equivalent to that in age-matched controls¹³. The finding of an improved survival rate for patients with good performance status has not previously been reported.

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Dismantling of a gastroenterostomy in the management of alkaline reflux gastritis

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Alkaline reflux gastritis is the most frequently encountered postgastrectomy syndrome requiring a remedial operation¹. The technique of loop gastrojejunostomy and truncal vagotomy has been shown to cause alkaline reflux gastritis more often than truncal vagotomy and pyloroplasty². Although not so frequently performed nowadays, a number of patients still exist who have undergone vagotomy and gastrojejunostomy and who may ultimately require operative treatment for alkaline reflux gastritis.

This paper presents experience with the simple dismantling procedure in six patients who had undergone vagotomy and gastrojejunostomy for benign ulcer disease and who later developed alkaline reflux gastritis.

Patients and methods

Between 1983 and 1989 four men and two women, aged 35–53 years, underwent truncal vagotomy and gastrojejunostomy in various centres for benign ulcer disease; 2–5 years later they presented with alkaline reflux gastritis refractory to medical treatment (Table 1). The most prominent complaints were dull and continuous epigastric pain and bilious vomiting. The duration of symptoms ranged from 1 to 4 years.

All patients underwent gastroscopy which demonstrated copious bile reflux and various degrees of mucosal erythema and friability, which was not limited to the peristomal area. There was no recurrent ulceration and no outlet obstruction. Biopsy findings were consistent with severe alkaline gastritis. Retained food fibres were also observed during endoscopy, although all patients had fasted for 12 h before the procedure. Barium meal showed that the passage of radio-opaque material through the gastroenterostomy was satisfactory.

The gastrojejunostomies were dismantled by the senior author (R.I.) and the remaining gastric and jejunal defects were primarily repaired in two layers. All patients were followed for a minimum of 30 (mean 42) months and were evaluated by endoscopy and Visick grading. All patients were also assessed by barium meal 1–2 months after reoperation.

Every patient had a dramatic improvement in symptoms after reoperation. None died and there was no morbidity except for a pulmonary infection in one. Results of the barium examinations were within normal limits in all patients and all were Visick grade 1 at last follow-up. There was no recurrent ulceration in any patient.

Discussion

The treatment of choice for patients with gastric resection who have alkaline gastritis is Roux-en-Y gastrojejunostomy, which

Table 1 Patient details

Patient no.	Age (years)	Sex	Duration of illness (years)	Type of gastroenterostomy
1	35	M	2	Antecolic
2	36	M	3	Retrocolic
3	38	F	1	Retrocolic
4	46	M	3	Antecolic
5	50	M	4	Antecolic
6	53	F	2	Retrocolic

gives satisfactory results in 60–80 per cent of cases. Nevertheless, this may still result in the so-called Roux syndrome in 15–30 per cent of patients³. There is a subgroup of patients whose initial operation was vagotomy and gastrojejunostomy. Although effective medical therapy and highly selective vagotomy have meant that this operation is now performed infrequently, it may still be used for benign ulcer disease from time to time.

Before proceeding with the more complex procedures (i.e. Roux-en-Y), simple dismantling of the gastrojejunostomy should be given serious consideration⁴. There must be no pyloric obstruction, no recurrent ulcer, and at least 1 year must have passed since the time of the initial operation for the stomach to have regained its tone^{1,4}. There are several advantages of this operation. The most important is the reinstitution of normal pyloric anatomy.

The patients discussed here have responded dramatically to such treatment, as did those in the small personal series of Alexander-Williams⁴, and all are currently leading a normal life with no problems of gastric emptying. The addition of pyloroplasty at reoperation is unnecessary if there is no pyloric stenosis and if more than 1 year has passed since the initial operation. It must also be appreciated that pyloroplasty might cause a recurrence of the alkaline reflux gastritis.

In summary, dismantling of a gastrojejunostomy is easy and effective. It should be considered for any patient with alkaline reflux gastritis after vagotomy and gastrojejunostomy if there is a patent pylorus, no recurrent ulcer, and if at least 1 year has passed since the initial operation. This may save some patients from developing an unnecessary Roux syndrome.

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Surgery in tropical pancreatitis: analysis of risk factors

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Over a 7-year period, 91 patients with tropical pancreatitis underwent operation for intractable pain. Univariate and multivariate analyses were performed to identify factors correlating with mortality, major complications, poor pain relief and associated malignancy. Patients with benign disease (group 1, n = 72) had longer survival than those with superimposed malignancy (group 2, n = 19). Pain relief was better in group 1 (59 patients compared with none, $P < 0.01$). Age above 40 years, short duration of symptoms, mass lesions on ultrasonography and main pancreatic duct obstruction on endoscopic retrograde pancreatography were associated with a high risk of cancer. After reoperation major complications (four of ten) or death (three of ten) occurred more commonly than after primary procedures (seven of 81, $P = 0.019$ and five of 81, $P < 0.05$, respectively). Poor pain relief in group 1 patients was more common after incomplete clearance of main duct stones (four of 13 versus three of 53, $P < 0.01$) and after short length ductotomy (three of eight versus four of 58, $P < 0.01$). Tropical pancreatitis has a high association with pancreatic adenocarcinoma. Wide ductotomy, stone clearance and drainage gave good symptomatic results in patients with benign disease. Overall results were poor in patients with cancer.

Tropical pancreatitis is a form of chronic pancreatitis that occurs in Asia, Africa and South America. It affects non-alcoholic individuals and is characterized by diabetes mellitus, pancreatic duct calculi and abdominal pain. The southern Indian state of Kerala has the highest incidence of this disease in the world¹. It was originally described as 'pain in childhood, diabetes in adolescence and death in the prime of life' by GeeVarghese² in 1968. Recent trends indicate a tendency towards older age at presentation, a lower operative mortality rate and better results of surgical attempts at pain relief^{1,3}. This has been due largely to better medical management of diabetes mellitus and preoperative delineation of the morphology of the ductal system by invasive and non-invasive methods⁴.

This paper outlines the preoperative evaluation, operative approach and results of surgery in patients with intractable pain due to tropical pancreatitis, and attempts to identify risk factors that correlate with postoperative and late death, major complications, poor pain relief and associated malignancy.

Patients and methods

Patients

A total of 262 patients with tropical pancreatitis presented to this clinic during the 7-year period June 1983 to May 1990. Of these, 102 patients (38.9 per cent) underwent operation. Eleven patients who consumed alcohol regularly in significant amounts were excluded from analysis despite the fact that they had pancreatic stones before taking alcohol. The remaining 91 patients were studied. There were 57 men and 34 women (M:F 1.7:1). The median age was 39 (range 10-60) years. Diabetes mellitus was present in 52 patients (57 per cent) and an additional 14 had abnormal glucose tolerance. Thirty-three patients (36 per cent) had symptomatic steatorrhoea before operation.

Ten patients had undergone previous surgery for abdominal pain. The operations performed were vagotomy and drainage ($n = 3$), gastroenterostomy ($n = 1$), retrograde pancreaticojejunostomy ($n = 1$),

cystogastrostomy ($n = 1$), transduodenal sphincteroplasty ($n = 1$), cholecystectomy ($n = 2$) and exploratory laparotomy ($n = 1$).

Diagnosis

Tropical pancreatitis was diagnosed if the patient did not regularly consume alcohol, and if two of the following criteria were present: (1) pancreatic calculi seen on abdominal radiography; (2) dilated main pancreatic duct on ultrasonography; or (3) pancreatographic evidence of changes indicative of chronic pancreatitis. Three patients who had acalculous disease had dilated ducts, and five with normal-calibre ducts had calculi (three of whom had tumours). Contrast imaging of the ductal system was achieved in 87 patients (the remaining four had tumours). Endoscopic retrograde pancreatography (ERP) was the preferred method and was successful in 79 patients. When ERP failed, preoperative ultrasonographically guided percutaneous pancreatography or operative ambigrade pancreatography was used to delineate the duct. Detailed imaging data are shown in Table 1. On imaging, all patients had marked changes associated with chronic pancreatitis as defined by Axon *et al.*⁵. Although 16 patients had biliary dilatation on ultrasonography, only eight were jaundiced. In the latter part of the study, computed tomography was used to evaluate pancreatic mass lesions in patients suspected of having malignancy.

Functional assessment

Glucose tolerance was assessed before operation and 3 months after operation by a standard oral glucose tolerance test or, in diabetics, by insulin requirement.

Patients were asked to assess whether they had returned to a normal lifestyle and whether they felt healthy or not.

Assessment of severity of pain

Severity of pain was assessed: grade 1, no symptoms; grade 2, occasional pain controlled easily by medication with no interference with work; grade 3, severe pain responding to medication but interfering with work; and grade 4, severe unrelieved pain.

Indications for surgery

All patients had intractable pain (grades 3 or 4). Significant weight loss (> 10 per cent of body-weight over 6 months) was present in 56 patients (62 per cent) and eight (9 per cent) were jaundiced.

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Table 1 Results of various imaging techniques in tropical pancreatitis

	Abdominal radiography	Ultrasonography	Pancreatography*	Computed tomography
No. of cases attempted	91	70	91	7
Successful imaging	91	70	87	7
Calculi	88	69	—	7
Localized	46	36	—	3
Extensive	42	33	—	4
Pancreatic duct				
Dilated	—	65	85	5
Normal calibre	—	—	2	2
Narrowing	—	—	21	—
Total block	—	—	38†	—
Cysts	—	12	6	—
Parenchymal mass	—	34‡	—	7
Biliary dilatation	—	16	14	2

*Endoscopic retrograde pancreatography ($n = 79$), percutaneous transhepatic cholangiography ($n = 4$), percutaneous pancreatography ($n = 7$), operative pancreatography ($n = 9$); eight patients underwent more than one procedure. †Includes 19 patients with histologically proven malignancy; ‡includes 19 patients with malignancy

Table 2 Operative procedures in 91 patients with tropical pancreatitis

Procedure	Group 1 (benign; $n = 72$)	Group 2 (malignancy; $n = 19$)
Drainage		
Lateral pancreaticojejunostomy (LPJ)	59	2
Pancreaticogastrostomy	3	7
Transduodenal pancreatic sphincteroplasty (TDPS)	1	—
LPJ and TDPS	6	—
Resection		
Pancreaticoduodenectomy	3	1
Distal resection		
Tail alone	10	—
75% distal pancreatectomy	—	4
Biopsy only	—	3
Cyst drainage		
Jejunum	8	—
Stomach	2	—
Duodenum	2	—
Choledochoduodenostomy	9	1
Choledochojejunostomy	—	2

Some patients underwent more than one procedure

Operative procedures

The aims of surgery were to clear the main duct of stones and to establish wide drainage of the pancreatic duct to the bowel, from the head to tail, along nearly its entire length.

Two distinct groups could be identified at operation: group 1 ($n = 72$) with benign disease and group 2 ($n = 19$) with tropical pancreatitis and associated tumours (proven histologically to be adenocarcinomas). The procedures performed are shown in Table 2.

Group 1. Lateral pancreaticojejunostomy (Partington-Rochelle modification of the Puestow-Gillesby procedure, LPJ) was the most common procedure used, being performed in 65 patients. In six of these, an additional transduodenal pancreatic sphincteroplasty (TDPS) was required to achieve stone clearance in the head region. Of the two patients in group 1 with normal-calibre ducts, one was managed by TDPS and the other by distal pancreatectomy with pancreaticogastrostomy. Pancreaticogastrostomy was also performed in two other patients with foreshortened glands, one of whom also had a leaking pseudocyst and pancreatic ascites.

Thirteen patients underwent pancreatic resection: ten by distal pancreatectomy and three by pancreaticoduodenectomy. Indications for distal pancreatectomy included stones lying above a tight stricture ($n = 3$), atrophic tail containing stones ($n = 2$), phlegmonous masses

with benign histology ($n = 4$) and abscess in the tail ($n = 1$). Drainage of the pancreatic remnant was by LPJ in nine patients and pancreaticogastrostomy in one. Three patients with predominant pancreatic head disease and biliary obstruction underwent pancreaticoduodenectomy. Reconstruction was by pancreaticogastrostomy in all cases. The remaining nine patients with benign biliary obstruction were managed by supraduodenal side-to-side choledochoduodenostomy.

Twelve cysts (13 per cent) were drained into the jejunum in eight patients, and to the stomach and duodenum in two cases each. Of the eight cystojejunostomies, five were incorporated with the LPJ and three were anastomosed separately. Cysts communicated with the pancreatic duct in seven patients.

Group 2. Tumours were located in the pancreatic head in four patients, in the body in nine and in the tail in five. One patient had an extensive tumour. In these patients, there was neither preoperative biopsy proof of cancer nor evidence of extrapancreatic spread on ultrasonography. Only five of 19 tumours could be resected (26 per cent), four by 75 per cent distal pancreatectomy, and one by pancreaticoduodenectomy. Two patients who underwent distal pancreatectomy also required resection of the transverse colon in one and of the transverse colon and stomach in the other. All tumours were advanced with considerable local and lymphatic spread. Eight patients had stage III and seven stage IV disease⁶. Liver metastases, present in seven patients, were small, multiple and widespread over both lobes of the liver. The remaining 14 patients underwent palliative procedures: pancreaticoenteric anastomosis in nine, biliary bypass in two and biopsy alone in three. These patients also underwent coeliac plexus block with absolute alcohol either at surgery or after operation by a percutaneous route.

All patients had pancreatic calculi in areas remote from the tumour or changes associated with chronic pancreatitis in the ductal system downstream from the tumour. This indicates that the ductal changes were not secondary to obstructive pancreatitis due to tumour and that pancreatic cancer had indeed developed in a setting of chronic pancreatitis (Figure 1). Histological examination of resected specimens showed features of chronic calcifying pancreatitis in areas well away from the tumour.

Follow-up

Five patients in group 1 and three in group 2 died after operation. Three patients were lost to follow-up (one in group 1 and two in group 2) leaving for analysis 66 patients in group 1 and 14 in group 2. The mean follow-up was 33 (range 7–87) months in group 1 and 10 (range 4–27) months in group 2.

Data analysis

Patient data were studied using univariate and multivariate analyses to determine risk factors correlating with mortality, major complications, poor pain relief and associated malignancy. Twenty-two variables were examined: age, sex, duration of pain, diabetes, jaundice, weight loss, previous operation, location of calculi, ultrasonographic evidence of mass, main pancreatic ductal obstruction on ERP, blood

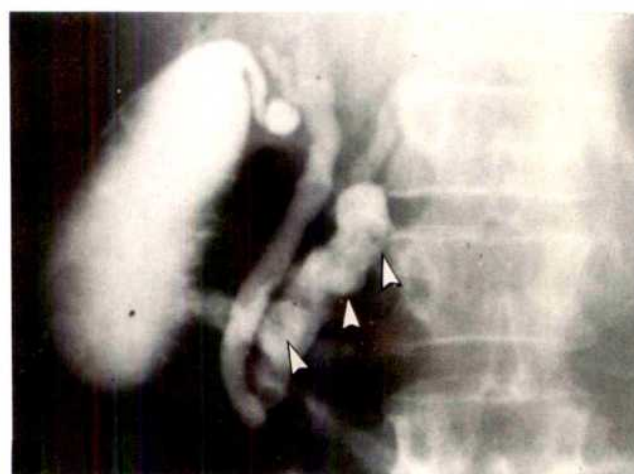


Figure 1 Appearances at endoscopic retrograde pancreatography of chronic pancreatitis with ductal block due to cancer. Note the radiolucent filling defects (stones) marked by arrows and the dilated ducts downstream from the tumour

group, serum amylase, albumin, bilirubin, gland size and texture at operation, presence of cyst, phlegmon or biliary obstruction, the extent of ductotomy, completeness of stone clearance and the presence of infected pancreatic fluid. Univariate analysis was performed using the χ^2 or Mann-Whitney *U* tests where appropriate. Multivariate analysis was performed using the Epidemiological Graphics, Estimation and Testing statistical package (Johns Hopkins University, Baltimore, Maryland, USA).

Results

Mortality rate

Major complications occurred in 11 patients (12 per cent), of whom eight (9 per cent) died. Five of these were in group 1 and three in group 2 (seven versus 16 per cent, *P* not significant). The complications were pancreatic anastomotic leakage (*n* = 3), adult respiratory distress syndrome (*n* = 3), renal failure (*n* = 1), hepatocellular failure (*n* = 1), diabetic ketoacidosis (*n* = 2) and septicaemia (*n* = 1).

In group 1, two patients died from adult respiratory distress syndrome. Two patients developed massive secondary haemorrhage as a result of major anastomotic leakage after LPJ; in both a near total pancreatectomy was performed and bleeding was controlled, but these patients died from systemic sepsis. The fifth patient died from renal failure secondary to diabetic nephropathy 22 days after surgery. The causes of death in group 2 patients were septicaemia, liver failure and adult respiratory distress syndrome in one patient each.

Survival

All 66 patients analysed in group 1 were alive after a mean follow-up of 33 months. In group 2, however, seven patients had died within 8 months of operation, leaving the remaining seven alive after a mean follow-up of 10 months. Survival was significantly better in patients with benign disease (*P* < 0.01). Survival in patients in group 2 undergoing resection was worse than in those who were not (8.2 versus 10 months).

Severity of pain before and after operation

Before operation, pain was assessed in 27 patients as grade 3 and in 64 as grade 4. After operation, patients in group 1 showed significant improvement (grade 1, 49; grade 2, ten; grade 3, six; grade 4, one) compared with group 2 where all patients remained in grade 3 or 4 (*P* < 0.01). Coeliac plexus block was performed in 14 patients, but provided pain relief in only seven, and the benefit was short-lived (mean 45 (range 16–142) days).

Reoperation

Five patients required reoperation, all in the benign group. Two of these were for abscesses in the head and tail of the gland presenting 38 and 4 months after surgery. Two others

presented with intestinal obstruction owing to adhesions and internal herniation at 7 and 8 months. The fifth patient underwent reoperation for persistent pain, but no abnormality was found.

Areas of failure

Seven patients had poor pain relief. Three had persistent pancreatitis in the head with phlegmons from failure to extend the ductotomy into the head (two of these three also had retained stones), and two others had poor clearance of the main duct of stones in the head and tail region. One patient who had undergone a pancreaticoduodenectomy had disabling steatorrhoea despite oral pancreatic enzyme therapy. A 20-year-old male university student had persistent abdominal pain despite complete stone clearance and wide LPJ. He finally underwent reoperation. The anastomosis was found to be widely patent and there was no other abnormality. After the second operation, he continued to have symptoms; these have been partly relieved by antidepressant drugs prescribed at another centre.

In the first 2 years of the study, pancreatic ductotomy was confined to 8–10 cm of the body. However, it became clear that persistent disease in the head and tail required reoperation (for abscesses) and also caused persistent pain. Thereafter, ductotomy was extended up to the tail and well on to the head of the pancreas to within 1 cm of the duodenum.

Functional results

All 66 patients in the benign group available for follow-up were assessed for alterations in exocrine and endocrine pancreatic

Table 3 Functional results after operation for tropical pancreatitis in group 1

Factor	No. of cases (<i>n</i> = 66)
Glucose tolerance	
Better	12 (18)
Same	44 (67)
Worse	10 (15)
Steatorrhoea	
Better	6 (9)
Same	42 (64)
Worse	18 (27)
Return to normal lifestyle	58 (88)
Wellbeing	
Healthy	46 (70)
Unhealthy	20 (30)

Values in parentheses are percentages

Table 4 Univariate analysis of risk factors against outcome

Factor	Mortality	Major complication	Associated malignancy	Pain relief	
				Overall (n = 80)†	Benign (n = 66)
Age over 40 years*	n.s.	n.s.	<0.01	n.s.	n.s.
Duration of pain under 1 year*	0.055	n.s.	<0.001	<0.01	n.s.
Weight loss	n.s.	n.s.	<0.01	<0.01	n.s.
Previous operation	n.s.	<0.05	n.s.	n.s.	n.s.
Extensive calculi	n.s.	n.s.	<0.01	n.s.	n.s.
Mass lesion on ultrasonography	n.s.	n.s.	<0.001	<0.001	n.s.
Main pancreatic duct obstruction on endoscopic retrograde pancreatography	n.s.	n.s.	<0.001	<0.001	n.s.
Serum albumin*	n.s.	n.s.	<0.01	n.s.	n.s.
Enlarged gland	n.s.	n.s.	<0.001	<0.001	n.s.
Oedematous gland	n.s.	<0.05	n.s.	n.s.	n.s.
Incomplete stone clearance from main pancreatic duct	n.s.	n.s.	<0.001	<0.001	<0.001
Short ductotomy	n.s.	n.s.	<0.001	<0.001	<0.001

Numbers are *P* values. Factors not significantly affecting outcome (sex, jaundice, diabetes, blood group, serum amylase, cyst, phlegmon, biliary obstruction, gland texture, infected pancreatic fluid) are excluded. n.s., Not significant; *Mann-Whitney *U* test; other factors, χ^2 test. †Eleven patients died or were lost to follow-up

Table 5 Multivariate analysis of risk factors

Outcome and factor	<i>P</i>	Odds ratio
Mortality		
Previous operation	0.023	1.9 (1.2-3.4)
Major complication		
Previous operation	0.036	2.2 (1.1-3.8)
Oedematous gland	0.040	1.5 (1.2-2.1)
Cancer		
Symptoms under 1 year	0.013	1.7 (1.4-4.6)
Mass lesion on ultrasonography	0.024	4.8 (2.7-6.1)
Duct obstruction on endoscopic retrograde pancreatography	0.034	2.5 (1.3-5.8)
Enlarged gland	0.008	2.8 (1.8-3.7)
Pain relief (n = 66)		
Poor stone clearance	0.029	2.3 (0.9-6.6)
Short ductotomy	0.016	3.1 (2.1-5.2)

Values in parentheses are 95 per cent confidence intervals. Factors not significantly affecting outcome are excluded

status and for changes in lifestyle and state of health. The results are shown in Table 3.

In group 1, 59 patients (89 per cent) had good pain relief (grades 1 or 2) after surgery. However, only 12 patients (18 per cent) had improvement in glucose tolerance and only six (9 per cent) had improvement in steatorrhoea. Although there was satisfactory relief of pain in most patients and 58 (88 per cent) returned to work, only 46 (70 per cent) felt that they were completely healthy.

Data analysis

Univariate analysis showed significant association between various risk factors and five measured outcomes (Table 4).

Mortality

Short duration of symptoms ($P = 0.055$ on univariate analysis) correlated with operative death. On multivariate analysis, only previous operation correlated with mortality rate (Table 5).

Major complications

An oedematous gland predisposed to complications such as

pancreatic leakage. Complications were also common after reoperation ($P = 0.019$) and in non-diabetics (20 versus 6 per cent in diabetics) although the latter difference was not statistically significant.

Associated malignancy

Ten factors significantly influenced the risk of associated malignancy on univariate analysis (Table 4). However, only short duration of symptoms, ultrasonographic evidence of a pancreatic mass, complete ductal obstruction on ERP and an enlarged gland at operation correlated with malignancy on multivariate analysis (Table 5). These factors were also present in some patients with benign disease (only 19 of 38 patients with ductal obstruction had malignancy). When ductal obstruction was absent, however, malignancy could be ruled out. The absence of these factors had considerable negative predictive value.

Pain relief after surgery

Pain relief was poor in patients with malignancy. Therefore, when all the survivors were studied, factors correlating with malignancy also correlated with poor pain relief. However, when patients with benign disease alone were studied, the operative technique was found to have a strong influence on the result (Table 4). Poor pain relief was associated with incomplete stone clearance from the main duct and a ductotomy stopping short of the head on both univariate and multivariate analyses.

Discussion

The aims of surgery in tropical pancreatitis, as in chronic pancreatitis caused by alcohol abuse, are to relieve intractable pain, to treat complications, especially if they are potentially life threatening, to preserve functioning pancreatic tissue and to perform surgery with low mortality and morbidity rates⁷. The high operation rate (38.9 per cent) in this series is due largely to referral of patients with intractable pain from other hospitals and does not reflect the true overall incidence of intractable pain.

Tropical pancreatitis is a primary ductal lithiasis. The stones may reach a large size of up to 4.5 cm in diameter³ and may also have dumbbell-shaped extensions into the side branches

that are difficult to remove at surgery. Clearance of these staghorn-shaped calculi from the main duct is necessary to allow free drainage of the side branches into the main duct. This can be achieved only by a long ductotomy extending from the tail to within 1 cm of the medial border of the duodenum. Failure to clear stones completely and a wide ductotomy stopping short of the pancreatic head correlated significantly with a poor result. A long LPJ has given good results in the present series. The mortality rate was low (7 per cent), with only one death in the last 45 patients, and parenchyma was preserved.

There are several other published results of LPJ in tropical pancreatitis^{8,9}. In many of these cases, preoperative identification of ductal morphology was not achieved and follow-up was incomplete. In the present series, duct morphology was a major guideline for deciding the type of operation and also the requirement for resectional surgery.

Although some reports favour pancreaticogastrostomy in both alcoholic and tropical pancreatitis¹⁰⁻¹², it is clear that, after the duct has been opened along its entire length, a long anastomosis to the posterior wall of the stomach from pylorus to fundus is often difficult. If there is anastomotic breakdown, combined leakage of pancreatic and gastric-biliary-intestinal juice occurs, whereas in a Roux-en-Y pancreaticojejunostomy the fistula is mainly pancreatic in nature. We have used pancreaticogastrostomy in patients with foreshortened glands and oedematous parenchyma as the anastomosis is easier to perform. Similarly, some surgeons have used TDPS alone, or in combination with pancreatic lithotomy and duct closure, with varying results^{3,8,13}. It is clear, however, that TDPS is at best an adjunct to wide ductotomy and LPJ in achieving clearance of stones and better drainage of the ducts in the head region. In this series, TDPS was used as a sole procedure in one patient with a duct of normal calibre.

There is some debate over the role of major pancreatic resection in patients with tropical pancreatitis. It may be argued that the sequelae of removal of a gland with extensive structural and functional damage may be acceptable and that removal of the gland also avoids the risk of synchronous and metachronous cancer³. There are several reports of pancreatic resection in alcoholic pancreatitis¹⁴⁻¹⁷. However, major pancreatic resection in malnourished patients with tropical pancreatitis is not an exercise to be undertaken lightly. Only three patients in the present series underwent major pancreatic resection for benign disease. All had biliary obstruction and disease predominantly in the pancreatic head. Surgery was effective in relieving pain, but disabling steatorrhoea and weight loss occurred. These patients regained their preoperative weight only 1 year after surgery, despite large doses of oral pancreatic enzymes. Conservative resection of the tail, on the other hand, could be achieved where indicated with very little loss of parenchyma. The good results obtained with long ductotomy, stone clearance and LPJ over a mean follow-up of 33 months support the policy of conserving pancreatic parenchyma whenever possible.

The pattern of biliary obstruction differed in the benign and malignant groups. Sixteen patients had biliary obstruction (12 benign and four malignant). Although all four patients with malignant obstruction had clinically apparent jaundice, only four of the 12 with benign obstruction were icteric ($P < 0.01$). The presence of jaundice in biliary obstruction due to tropical pancreatitis is suggestive of malignancy. Similar data have been reported by Chari *et al.*¹⁸.

Nerve interruption procedures were not used in any of the present patients with benign disease. Although encouraging early data have been reported in the literature, results of adequate follow-up are not yet available¹⁹. Percutaneous chemical block of the coeliac plexus was used in this series only in patients with malignancy. Relief occurred in only half of the patients and was transient.

Over the past decade, there has been increasing evidence of an association between tropical pancreatitis and pancreatic adenocarcinoma^{18,20-22}. Of 91 patients in this series, 19

(21 per cent) had associated malignancy. These patients constitute a high-risk group with poor pain relief and short survival. In our experience, the diagnostic yield of percutaneous or even operative Tru-Cut (Travenol Laboratories, Deerfield, Illinois, USA) needle or shave biopsies was poor; proof of malignancy was available only at autopsy. Therefore an aggressive policy was adopted, with resection of these tumours wherever possible, despite extrapancreatic spread. Although there were no deaths in the group undergoing resection, this procedure did not improve survival.

It is not clear whether tropical pancreatitis predisposes to malignant change or whether the two conditions merely coexist. Hospital-based statistics indicate that the incidence of exocrine pancreatic cancer in southern India is low (1.3 per cent of all cancers in men and 1.1 per cent in women). It appears that malignancy in tropical pancreatitis is an entity clinically distinct from cancer arising *de novo* and that there may well be a genetic or environmental basis as shown by the occurrence of tropical pancreatitis and cancer in siblings²².

In conclusion, a long ductotomy, stone clearance and LPJ gives good relief of pain in patients with tropical pancreatitis. Presence of associated malignancy carries a poor prognosis and can be identified before operation by the short duration of symptoms, the presence of a pancreatic mass on ultrasonography and duct obstruction at ERP.

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Announcement

Peter Clifford Travelling Scholarship

Applications are invited for the second annual Travelling Scholarship (£1000) set up in memory of Peter Clifford MD FRCS (1949-1989), Consultant Surgeon, Frenchay Hospital, UK.

The purpose of the Scholarship is to enable a UK or Irish trainee surgeon to visit a vascular unit overseas and then to deliver the Peter Clifford Memorial Lecture in a surgical forum on his or her return.

Further details can be obtained from: Mr Peter McDonald, Consultant Surgeon, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, UK.

Endoscopic sphincterotomy in young patients with choledochal dilatation and a long common channel: a preliminary report

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An anomalous elongated pancreaticobiliary common channel encourages reflux up both the biliary tree and the pancreatic ductal system, resulting in progressive choledochal dilatation, cholangitis with ductal calculi, relapsing pancreatitis and malignant change. Transduodenal sphincteroplasty has been used to improve drainage from the abnormal channel. The use of endoscopic sphincterotomy (ES) to establish drainage and minimize the surgical risks is reported in six symptomatic patients with mild choledochal dilatation (common bile duct diameter <15 mm), a common channel <15 mm in length and a distal stenosis. This was successful in five patients, who have no further symptoms. ES failed in the only patient with an undilated common channel and this patient went on to have open surgery. We believe ES to be safe and effective in the treatment of selected cases of long common channel.

A long common pancreaticobiliary channel is correlated with a range of choledochal dilatation from minimal fusiform distensions to gross cystic enlargement¹⁻³. There is general agreement on the surgical management of choledochal cysts by total cyst excision and bilioenteric drainage, but it is not clear whether it is justifiable to subject all patients with minimal and diffuse choledochal dilatation to the same procedure. Todani *et al.*⁴ have reviewed this problem extensively and suggested that transduodenal sphincteroplasty is the treatment of choice for type IC dilatation. Takiff *et al.*⁵ raised the suspicion that patients with the uncommon, mildly dilated, fusiform 'choledochal cyst' might benefit less from wide excision of the involved bile duct. A new application of endoscopic sphincterotomy (ES) in the treatment of selected cases of cylindrical bile duct dilatation associated with pancreaticobiliary ductal malunion is reported.

Patients and methods

ES was performed in six children (Table 1). All presented primarily with abdominal pain and hyperamylasaemia, which was gross (over four times the upper limit of normal) in four and moderate (over twice the upper limit of normal) in two. Criteria for selecting patients for ES

were: common bile duct (CBD) diameter ≤ 15 mm in at least one measurement; common channel <15 mm in length; and narrowing, if present, located at the distal end of the common channel. Indications were: unrelenting pancreatitis with unremitting hyperamylasaemia (one patient); cholangiopancreatitis with fever (one patient); obstructive jaundice (one patient); and relapsing pancreatitis (three patients). All procedures were undertaken under general anaesthesia except for the first ES in patients 4 and 6: the 10-year-old girl was deemed old enough to cooperate, and for the other patient general anaesthesia was not available in the radiography suite at the time of the examination. Olympus duodenoscopes JF IT10 or JF IT20 (Olympus, Tokyo, Japan) were used without difficulty.

Completeness of sphincterotomy was demonstrated by: prompt emptying of contrast from both the biliary and pancreatic ductal systems on assuming the upright posture; gas in the biliary tree; widening of the previously noted distal narrowing preferably up to the widest diameter of the channel (Figure 1); and/or exposure of the openings of the CBD and the pancreatic duct separately into the duodenum (Figure 2). Success was determined clinically by rapid relief of pain, fever and jaundice, together with a return to normal biochemical parameters, in particular serum amylase level. Ultrasonographic evidence of decreasing bile duct distension was also noted.

All these patients continue to undergo close long-term follow-up and regular ultrasonographic monitoring. Non-operative treatment is continued only when the CBD remains mildly dilated and remission of symptoms is sustained.

Table 1 Features of six patients with fusiform choledochal dilatation who underwent endoscopic sphincterotomy

										CBD diameter (mm)		Intrahepatic duct dilatation		
Patient			Presentation			Common channel								
No.	Sex	Age (years)	Pain	Bilirubin (μmol/l)*	Amylase (units/l)*	Length (cm)	Dilatation	Site of stenosis	No. of calculi	Before ES	After ES	Before ES	After ES	Symptoms after ES
1	F	3	Recurrent, moderate	27	1375	1.2	+	Distal	0	12-17	8	+	Mild	None
2	F	1.8	Once, mild	22	538	0.8	+	Distal	2	12-19	12	Mild	—	None
3	M	3	Recurrent, severe	38	1153	1.2	+	Distal	3	8-16	6	+	—	None
4	F	10	Recurrent, severe	243	620	1.0	+	Distal	5	14-22	8	+	Mild	None
5	F	5	Recurrent, moderate	30	368	0.8	+	Distal	0	8-10	5	+	—	None
6	F	4	Frequent, mild	7	248	0.9	—	—	0	10-21	25	+	+	Open surgery

CBD, common bile duct; ES, endoscopic sphincterotomy; *normal values: bilirubin <20 $\mu\text{mol/l}$; amylase <115 units/l



Figure 1 **a** Endoscopic retrograde cholangiopancreatography of patient 1 before sphincterotomy showing a dilated common channel (arrow). **b** Spot film taken in the upright position showing rapid emptying of contrast from the bile duct, total clearance of contrast from the pancreatic duct (PD), air in the biliary tree and widening of distal common channel following adequate sphincterotomy

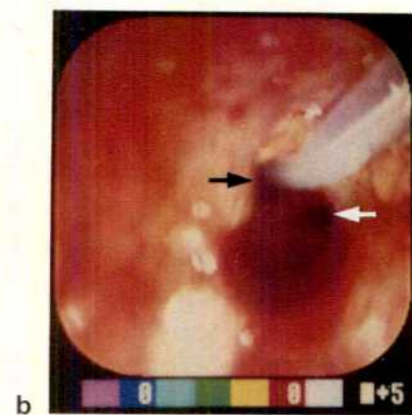


Figure 2 **a** Endoscopic retrograde cholangiopancreatography of patient 4 showing a wide common channel (arrow) with distal narrowing. **b** Duodenoscopic visualization of separate openings of the common bile duct (black arrow) and pancreatic duct (white arrow), made possible by a wide sphincterotomy

Results

Eight ES procedures were performed in six patients. None required preliminary needle knife sphincterotomy. Patients 4 and 6 were subjected to two ES operations each. Patient 4 developed upper gastrointestinal bleeding 6 days after the first ES. Emergency duodenoscopy revealed continuous oozing from lacerations on the oedematous duodenal papilla, apparently caused by an impacted stone emerging from the papilla. The stone was extracted and the sphincterotomy was extended. This

was followed immediately by cessation of bleeding and relief of all symptoms. ES was first attempted on patient 6 under heavy sedation, but the procedure had to be abandoned after making a small cut because the child was struggling. One week later repeat ES was performed under general anaesthesia, but despite diligent manipulation under screening, there was success in cutting only the distal half of the curved common channel which was narrow and undilated. Prompted by the ultrasonographic evidence of increased dilatation of the CBD to

2.5 cm in the ensuing month, it was decided to perform excision of the CBD followed by Roux-en-Y hepaticojejunostomy. In the 2 years since operation, this patient has continued to thrive. This is the only patient with hyperamylasaemia after sphincterotomy.

Five of six children recovered from the procedure without incident and have remained free from further attacks of pancreatitis or cholangitis for a mean of 4 (range 1.5–6.5) years, while their bile ducts have remained slightly dilated.

Discussion

Pancreaticobiliary ductal malunion is a developmental anomaly seen mostly in orientals^{1–5}. Characteristically, the pancreatic duct and the bile duct join at an unusually long distance from the duodenal papilla and the choledochal sphincter at the distal end of the CBD is hypoplastic², which allows free reciprocal reflux of bile and pancreatic juice. Clinically, a common channel may present with choledochal dilatation, intrahepatic cysts, obstructive jaundice, cholangitis, malignant degeneration and pancreatitis, either singly or in various combinations^{2,6–8}. Cases have been recognized in which there is only mild biliary dilatation and the cystic component is absent, especially during the quiescent phase^{6,9,10}. This kind of malformation has been designated forme fruste choledochal cyst⁹, a variant of conventional choledochal cyst. The common aetiological factor in this wide spectrum of malformations is believed to be the common pancreaticobiliary channel. It therefore seems reasonable to target this area for treatment.

Cutting open the common channel and its investing musculature effectively prevents pancreaticobiliary reflux, thereby averting all its ill effects. As exemplified by patient 4, ES did 'open up' the common channel, so that separate openings of the bile and pancreatic ducts were exposed (Figure 2b). This is feasible only in those few patients in whom the common channel is widely dilated and not too long (Figure 2a). However, in most cases, cutting open the stenosis only at the distal end of the channel can be achieved, with a view to promote free orthograde flow. Fortunately, fusiform choledochal dilatation, as opposed to cystic dilatation, has been observed to be more commonly associated with low grade, short strictures located at or distal to the pancreaticobiliary junction^{1,11}. Fusiform dilatation is also related to the formation of primary biliary stones¹². Choledocholithiasis and oriental cholangitis have been repeatedly shown to be eminently treatable by ES in conjunction with stone extraction^{13–15}.

There are limitations to ES. In light of the unpleasant experience with patient 6, dilatation of the common channel is now included in the selection prerequisites; ES is also not recommended as a definitive treatment for gross cystic dilatation in view of the significant risk of malignant degeneration in the cyst wall¹⁶. In contrast, carcinoma seldom, if ever, develops in fusiform dilatation¹⁰.

Endoscopic intervention is appealing since the child is spared an open operation. Early results are encouraging. Long-term results are not known, as longest follow-up barely exceeds 6.5 years. The present regimen mandates life-long, careful follow-up and is not advocated for patients with poor compliance. Late stenosis of the sphincterotomy and possible stone formation in the malfunctioning gallbladder are the two major long-term

concerns. Restenosis can be treated by another ES. None of the patients in this study has developed gallstones. If they did, extracorporeal shockwave lithotripsy would be helpful in the presence of patent cystic duct and wide sphincterotomy.

In conclusion, ES offers an alternative to surgical resection of the bile duct in children with fusiform bile duct dilatation and a long common pancreaticobiliary channel.

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Body water compartments in patients with obstructive jaundice

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To elucidate the pathogenesis of renal dysfunction associated with obstructive jaundice, body water compartments were measured using a multi-isotope dilution technique in ten patients with biliary tract obstruction and in ten control subjects matched for age, sex, weight, height and body surface area. Expressed as a fraction of body-weight, total body water was reduced in jaundiced patients (41.8 versus 46.2 per cent, $P < 0.02$). Extracellular water volume was also reduced in patients with jaundice (20.3 versus 24.3 per cent, $P < 0.003$) owing to a reduction of the interstitial space (16.1 versus 19.5 per cent, $P < 0.004$) and, to a lesser degree, of the plasma volume (4.2 versus 4.8 per cent, $P = 0.1$). There was a close correlation in jaundiced patients between plasma volume and the creatinine clearance rate ($r^2 = 0.56$, $P < 0.02$) and between plasma volume and extracellular volume ($r^2 = 0.77$, $P < 0.0001$). Extracellular volume in such patients also correlated with the percentage weight loss ($r^2 = 0.42$, $P = 0.04$). Obstructive jaundice is associated with a contracted extracellular water compartment, although extracellular water, as a percentage of body-weight, increased in proportion to the body-weight lost. Reduction of the interstitial volume and a marginally reduced plasma volume may be determinant factors in the pathogenesis of the renal and haemodynamic disturbances observed in patients with biliary tract obstruction.

At the beginning of this century the relationship between obstructive jaundice and renal failure was firmly established on clinical grounds^{1,2}. Currently, the incidence of this complication in patients undergoing surgery for the relief of biliary obstruction is between 6 and 18 per cent, with a 32–100 per cent mortality rate^{3–5}. Multiple hypotheses have been put forward to explain the mechanisms linking bile duct obstruction and renal dysfunction. These include perioperative renal ischaemia⁶, bilirubin toxicity⁷, endotoxaemia due to increased intestinal absorption of bacterial endotoxin in the absence of bile salts^{8,9}, decreased reticuloendothelial activity^{10,11}, microcirculatory disturbances secondary to altered prostaglandin synthesis^{12,13}, and myocardial depression¹⁴. Several approaches have been used to prevent the complication^{9,15–18} but none has gained widespread acceptance as all have yielded discordant results when submitted to clinical trials^{19,20}.

Hypovolaemia was once supposed to be an important factor in the pathogenesis of acute renal failure in experimental obstructive jaundice² and some clinical and experimental observations^{21–23} indirectly support this hypothesis. However, there have been no studies to document precisely the fluid status of patients with obstructive jaundice. Previous work by this group²⁴ showed that rabbits submitted to common bile duct ligation experienced a reduction in their extracellular water compartment and plasma volume. Accordingly, the present study was set up to investigate the size of water compartments in patients with obstructive jaundice.

Patients and methods

The study group included ten patients with obstructive jaundice. All had conjugated hyperbilirubinaemia with levels ranging between 150 and $545 \mu\text{mol l}^{-1}$ (mean(s.d.) $320(125) \mu\text{mol l}^{-1}$) and bile duct dilatation on abdominal ultrasonography and cholangiography (either transhepatic or retrograde). Furthermore, a definitive diagnosis was established at laparotomy. The patients had lost between 4 and 15 per cent (mean(s.d.) $9(3)$ per cent) of their usual body-weight.

Patients with cholangitis or with a history of hypertension, known renal dysfunction or diabetes mellitus were excluded from the study. Ten patients with benign surgical conditions and no weight loss, matched for age, weight, height, body surface area and sex served as the control group. There was one sex mismatch since a suitable female control could not be found; a woman in the study group (weight 53.5 kg) was matched with a man of similar age but lower weight (44 kg) to compensate for the slightly higher volume of the extracellular water in men. Patients had not received intravenous fluids for at least 1 week before the investigation. Details of both groups are shown in Table 1.

Blood creatinine, creatinine clearance and urea were measured in all patients. Informed oral consent was obtained from all subjects. Body composition analysis was carried out using the multi-isotope dilution technique of Bauer *et al.*²⁵ after an overnight fast. No invasive procedures had been performed in the jaundiced patients before body composition analysis. For the determination of total body water, extracellular water and plasma volume, the following isotopes were used: $^3\text{H}_2\text{O}$ (Ire Medgenix, Brussels, Belgium), $^{35}\text{SO}_4^{2-}$ and ^{125}I -radiolabelled albumin (Amersham International, Amersham, UK). A volume of 0.5 ml tritiated water (90 μCi , 3.3 MBq) and radiolabelled albumin solution (75 μCi , 2.8 MBq) was injected first through an antecubital vein. Thirty minutes later, a blood sample was taken on to ethylene diamine tetra-acetic acid from the contralateral forearm. Plasma was separated promptly and deproteinized by adding 10 per cent trichloroacetic acid (TCA: 2 ml plasma per 4 ml TCA). This plasma sample was used to measure the ^3H and $^{35}\text{SO}_4^{2-}$ radioactivity. Immediately after this, 0.5 ml ^{125}I -radiolabelled albumin solution (10 μCi , 0.4 MBq) was injected and blood samples were obtained at 10, 20 and 30 min for counting ^{125}I radioactivity after dilution in distilled water. The combined doses approximate to 1.5 mGy which is equivalent to the radiation exposure of a chest radiograph²⁵.

To determine the total radioactivity of administered ^3H and $^{35}\text{SO}_4^{2-}$, standard solutions were prepared by diluting doses (identical to those administered) of the isotope solutions in 1000 ml distilled water with a similar degree of quenching. Then, 1 ml of this solution was diluted twice 1:5 (final dilution 1:25 000) so that the counts would be similar to that of the serum samples. The ^{125}I standard was prepared by diluting a dose identical to that administered in 1000 ml distilled water. All the counting procedures (disintegrations per minute) were carried out in triplicate. ^3H and $^{35}\text{SO}_4^{2-}$ radioactivities were read after dissolving the deproteinized serum samples in 13 ml scintillation liquid

Table 1 Details of patients with obstructive jaundice and control patients matched for age, sex, weight, height and body surface area

	Age (years)	Sex	Weight (kg)	Height (cm)	Body surface area (m ²)	Diagnosis
Study group (n = 10)	80	F	63.7	144	1.54	Cholelithiasis
	50	F	84.5	149	1.79	Bile duct carcinoma
	78	M	69.1	152	1.66	Metastatic nodes
	71	M	65.5	162	1.70	Bile duct carcinoma
	64	M	72.3	172	1.85	Bile duct carcinoma
	84	F	52.0	152	1.46	Cholelithiasis
	88	F	56.0	155	1.54	Bile duct carcinoma
	69	F	53.5	137	1.38	Pancreatic cancer
	63	F	55.5	155	1.54	Bile duct carcinoma
	75	F	54.0	150	1.49	Pancreatic cancer
Mean(s.d.)	72(11)		62(10)	152(9)	1.60(0.1)	
Control group (n = 10)	81	F	54.5	149	1.47	Cholelithiasis
	56	F	70.5	160	1.75	Hiatus hernia
	72	M	72	169	1.82	Inguinal hernia
	87	M	50	152	1.46	Duodenal ulcer
	59	M	72	172	1.85	Inguinal hernia
	80	F	48.5	147	1.40	Villous adenoma
	79	F	62	153	1.60	Femoral hernia
	63	F	56	142	1.45	Cholelithiasis
	86	F	59	150	1.54	Femoral hernia
	64	M	44	151	1.38	Inguinal hernia
Mean(s.d.)	72(11)		58.8(10)	154(10)	1.57(0.1)	

(Scintiran; BDH, Poole, UK) in a LKB 1217 Rackbeta (Wallac, Turku, Finland). ³H and ³⁵SO₄²⁻ were counted by simultaneous β-counting using a liquid scintillation counter with correction for the contribution of the higher energy ³⁵S in the tritium channel. ¹²⁵I-radiolabelled albumin radioactivity was read on a Packard 800 C counter (United Technologies Packard, California, USA). Body water compartments were calculated using the following formulae in which a Donnan factor of 0.9 and a water protein content of 0.93 were assumed. In the first two formulae, the value 3 in the denominator represents the TCA dilution coefficient:

$$\begin{aligned} \text{Total body water (ml)} &= \frac{\text{d.p.m. per ml } ^3\text{H}_2\text{O (standard)} \times 25\,000 \text{ ml} \times 0.93}{\text{d.p.m. per ml } ^3\text{H}_2\text{O (plasma)} \times 3} \\ \text{Extracellular water (ml)} &= \frac{\text{d.p.m. per ml } ^{35}\text{SO}_4 \text{ (standard)} \times 25\,000 \text{ ml} \times 0.93 \times 0.9}{\text{d.p.m. per ml } ^{35}\text{SO}_4 \text{ (plasma)} \times 3} \\ \text{Plasma volume (ml)} &= \frac{\text{c.p.m. per ml } ^{125}\text{I-albumin (standard)} \times 1000 \text{ ml}}{\text{c.p.m. per ml } ^{125}\text{I-albumin (plasma)}} \end{aligned}$$

Intracellular and interstitial water values were obtained indirectly from the measured compartments. Water compartment volumes were expressed as a percentage of body-weight.

Results were analysed with the Statview II statistical package (Abacus Concepts, Berkeley, California, USA) using a Macintosh II (Apple Computers, Cupertino, California, USA). Student's two-tailed *t* test for unpaired samples was used. Correlations between variables were investigated using Pearson's correlation coefficient (*r*). Statistical significance was accepted when *P* < 0.05. All data are expressed as mean(s.d.).

Results

Details of both groups of patients are shown in Table 1. There were no significant differences in mean age, body-weight, height or body surface area. Blood biochemistry findings are shown in Table 2. The creatinine clearance rate for jaundiced patients ranged between 0.26 and 1.2 ml s⁻¹ (mean(s.d.) 0.71(0.31) ml s⁻¹) and was below 1 ml s⁻¹ in 77 per cent of the subjects.

The volumes of the different water compartments, expressed as a percentage of actual body-weight, are shown in Table 3. Total body water was reduced in the study group at the expense of the extracellular water compartment. The intracellular water compartment was similar in both groups. In the study group, there was a close correlation between plasma volume and creatinine clearance (Figure 1). Plasma volume was also closely correlated with extracellular water in the study group but not in the control group (Figure 2). In the study group, the percentage of body-weight lost correlated positively with

Table 2 Blood biochemistry findings in the study and control groups

	Study group	Control group	P*
Haemoglobin (g l ⁻¹)	122(10)	129(15)	n.s.
Urea (mmol l ⁻¹)	7.10(2.20)	5.58(1.22)	0.06
Creatinine (mmol l ⁻¹)	106(20)	91(11)	n.s.
Glucose (mmol l ⁻¹)	6.23(0.71)	5.51(0.45)	0.05
Albumin (g l ⁻¹)	32(5)	37(3)	<0.05
Sodium (mmol l ⁻¹)	135(5)	139(3)	<0.05
Creatinine clearance rate (ml s ⁻¹)	0.71(0.31)	0.92(0.33)	n.s.

Values are mean(s.d.). n.s., Not significant; *Student's *t* test

Table 3 Size of body water compartments, expressed as a percentage of actual body-weight, in the study and control groups

	Study group	Control group	P*
Total body water	41.8(3.3)	46.2(4.2)	<0.02
Extracellular water	20.3(2.5)	24.3(2.5)	<0.003
Plasma volume	4.2(0.8)	4.8(0.7)	n.s.
Interstitial water	16.1(1.9)	19.5(2.7)	<0.004
Intracellular water	21.7(5.2)	21.8(2.8)	n.s.

Values are mean(s.d.). n.s., Not significant; *Student's *t* test

extracellular water which, in turn, correlated inversely with serum albumin concentration (Figure 3). There was no correlation between the degree of extracellular water depletion and the serum concentration of total bilirubin or the duration of jaundice.

Discussion

Early studies of the pathogenesis of renal dysfunction associated with obstructive jaundice underlined the predisposition to hypotension and shock of patients undergoing surgery for the relief of biliary obstruction. The kidneys of patients dying from acute renal failure showed histopathological changes similar to those observed in hypovolaemic shock²⁶. Williams *et al.*² found that 6–8 weeks after bile duct ligation in dogs, plasma volume had decreased by 19 per cent. These authors also suggested that the weight loss observed in the jaundiced animals could be

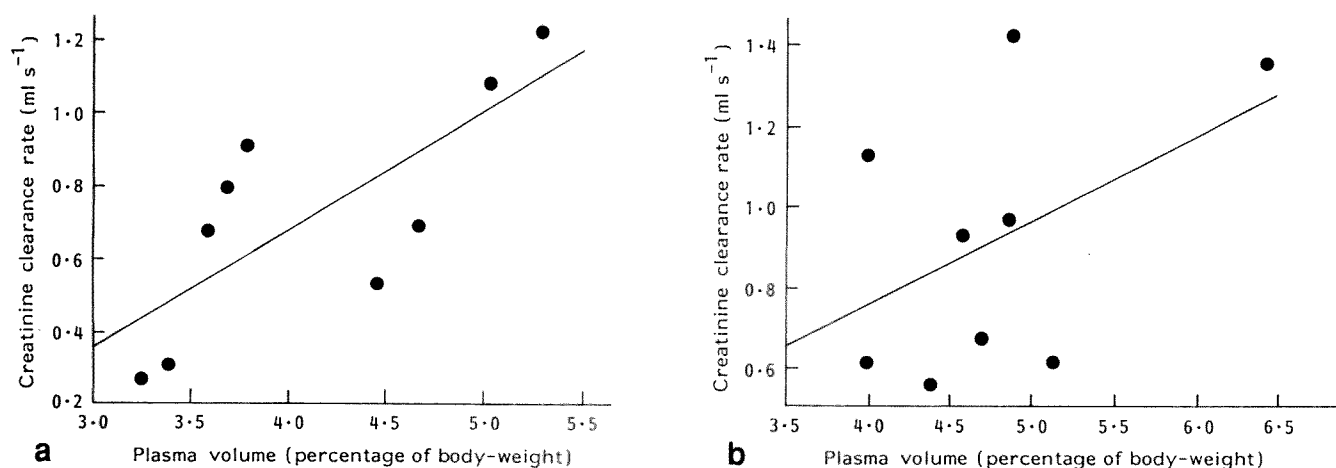


Figure 1 Correlation between creatinine clearance rate and plasma volume in **a** the study group ($r^2 = 0.56$, $P = 0.02$) and **b** the control group ($r^2 = 0.21$, $P = 0.21$). For technical reasons, the plasma volume could not be measured in one patient in each group. A higher correlation was found in jaundiced patients with water depletion

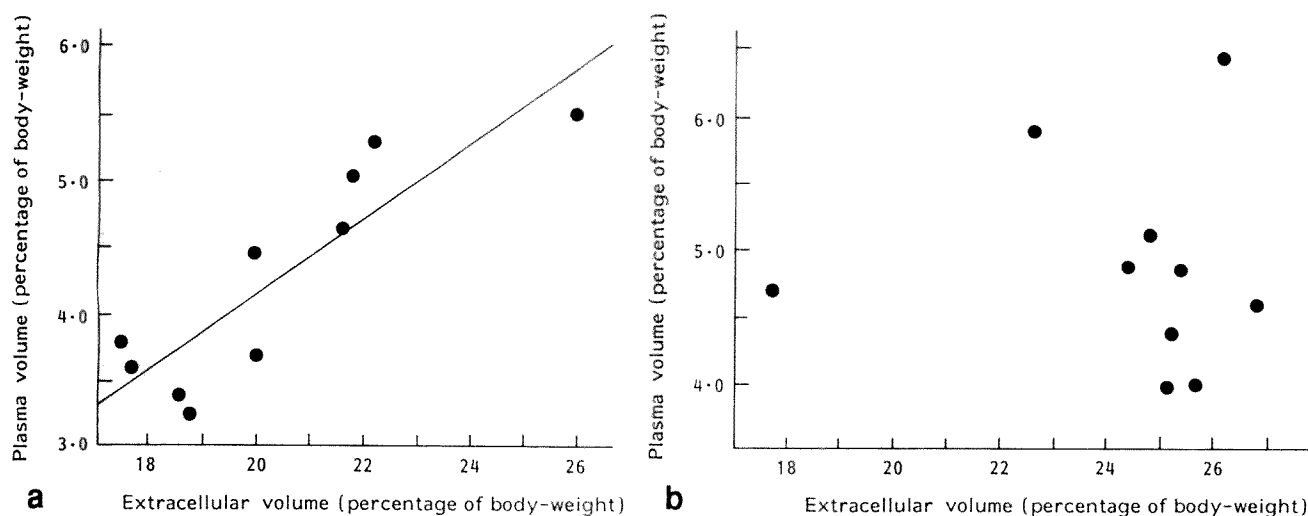


Figure 2 Correlation between plasma volume and extracellular volume in **a** the study group ($r^2 = 0.77$, $P < 0.0001$) and **b** the control group ($r^2 = 0.001$, $P = 0.9$)

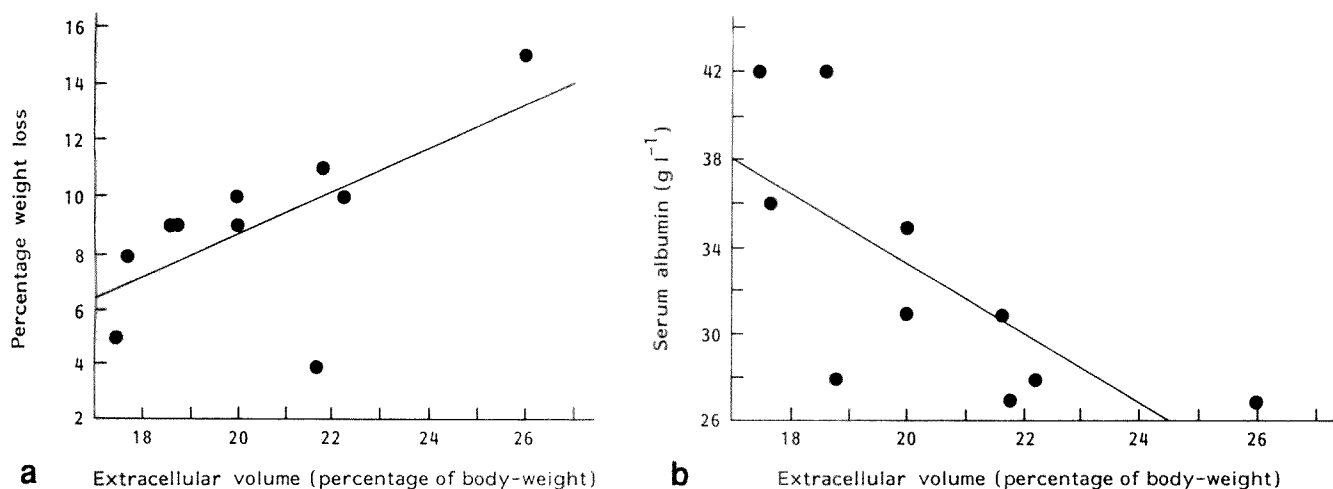


Figure 3 Correlations in the study group between **a** percentage weight loss and extracellular volume ($r^2 = 0.42$, $P = 0.04$) and **b** serum albumin level and extracellular volume ($r^2 = 0.5$, $P = 0.02$)

related to loss of body fluids. Gillet²² and Yarger *et al.*²³ also showed a reduction of plasma volume in rats after bile duct ligation. To our knowledge the only study which measured plasma volume in humans²¹ reported blood volume under a variety of surgical conditions. The authors stated that obstructive jaundice caused a reduction in plasma volume but did not support this assertion with appropriate data.

Martínez-Ródenas *et al.*²⁴ published the first comprehensive investigation on body water compartments in experimental obstructive jaundice using the same multi-isotope dilution technique employed in the present report. They used the rabbit as experimental model, since bile duct ligation in the rat or dog is commonly followed by ascites. Compared with sham-operated controls, rabbits with obstructive jaundice

showed a progressive decrease of the extracellular water compartment, with a loss of 24 per cent of basal values at day 6 and 35 per cent at day 12, which correlated closely with weight loss over the first 12 days of jaundice. At the end of this period, a 15 per cent reduction in plasma volume was observed. These experimental results broadly agree with the results of the present study. In humans with obstructive jaundice, the volume of the extracellular water compartment was 80 per cent of that of matched healthy controls, whereas in the rabbit with bile duct ligation it was 70 per cent. In both the human and animal experiments, the intracellular water compartment showed no changes. The reduction in the extracellular compartment was due mostly to a contraction of the interstitial space with preservation of the plasma volume. This is consistent with the data obtained during the early phases of experimental obstructive jaundice; plasma volume was preserved, only to fall in more advanced stages. Thus, it appears that in established obstructive jaundice, humans are more capable than rabbits of retaining free water. This is supported by the lower albumin and serum sodium concentrations, and the correlation between serum albumin and extracellular volume found in the study group only, which suggests some degree of haemodilution.

Malnutrition induces a relative expansion of the extracellular water compartment²⁷. Since jaundiced patients had lost a mean of 9 per cent of their usual body-weight, this may partially account for the close positive correlation observed between weight loss and extracellular water volume. The intracellular water compartment was similar in both groups, which suggests that weight loss in the study group was probably due to losses of both extracellular water and fat, but not lean body-mass. In fact, the data are consistent with the hypothesis that the reduction of extracellular water in obstructive jaundice is the result of two opposing effects: a negative water and sodium balance associated with bile duct obstruction *per se* and a relative extracellular fluid expansion due to the effect of malnutrition and weight loss. Accordingly, the adverse prognostic value of hypoalbuminaemia in patients undergoing surgery for obstructive jaundice²⁸ should be interpreted in the light of the disturbances of body water compartments demonstrated here.

The finding of a decreased extracellular space in obstructive jaundice agrees with reports suggesting that biliary obstruction leads to negative water and sodium balance secondary to reduced water intake and the inability of 'jaundiced kidneys' to concentrate the urine appropriately^{23,24,29-32}. Atrial natriuretic peptide levels are increased in experimental obstructive jaundice³⁰ and this humoral mediator is implicated as the most likely cause of the derangements of water and sodium metabolism associated with obstruction of the biliary tract.

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Elective hepatic resection in the elderly

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This retrospective review assessed the safety and validity of elective liver resection in patients older than 64 years of age. In all, 293 patients underwent elective liver resection over a 23-year period (1967-1990). Fifty-two patients (18 per cent) were older than 64 (maximum 84, mean 70.4) years and all but four of these did not have cirrhosis. In this older subgroup, indications for resection were liver metastases in 30 patients, primary malignancy in 16, benign tumours in five and multiple abscesses in one. There were 21 major resections, with two deaths from hepatic failure, and 31 minor resections, with one death from cardiac failure (total mortality rate 6 per cent). During the same period, there were seven deaths after elective resections performed in 222 patients without cirrhosis who were younger than 64 years ($P = 0.39$). Mortality rate and duration of postoperative hospital stay were not related to the extent of liver resection nor to patients' grading according to the American Society of Anesthesiologists' criteria. Intraoperative blood loss was the only parameter found to influence mortality rate ($P = 0.008$) and duration of hospital stay ($P = 0.04$). Elective liver resection can be safely undertaken in elderly patients without cirrhosis, provided that intraoperative blood loss is minimized.

Advances in liver surgery and the increasing proportion of elderly patients have encouraged hepatic resection in this population. Fortner and Lincer¹ reported an 11 per cent mortality rate in patients aged over 64 years (usually from hepatic failure) and Yanaga *et al.*² a rate of 41 per cent for elderly patients with hepatocellular carcinoma. Ezaki *et al.*³ showed that mortality in patients older than 66 years was due to intraoperative blood loss and postoperative hepatic failure. This retrospective study assessed the validity of elective hepatic resection in elderly patients and identified other risk factors associated with this type of surgery.

Patients and methods

Between 1967 and 1990, 293 elective hepatic resections were performed. Fifty-two patients (18 per cent) were older than 64 years; four of these had cirrhosis. Eighteen of these patients were operated on before 1982 and 34 since 1982. Latterly the Pringle manoeuvre, triple clamping and ultrasonic dissection were used. Mortality rates and intraoperative blood transfusion were compared between these two periods. Data collected included sex, age, diagnosis, preoperative grading using the criteria established by the American Society of Anesthesiologists (ASA)⁴, type of resection performed, intraoperative blood transfusion, postoperative complications, in-hospital mortality and duration of hospitalization. These data were complete for 88 per cent of patients. The extent of hepatectomy was classified according to Couinaud⁵. No patient was excluded for being unfit to withstand liver resection. Preoperative selection was made by the patient's physician before hospitalization. Patients graded ASA III and IV were not rejected for surgery if still physically active.

Data were compared using Fisher's exact two-tailed test, χ^2 test and Student's *t* test. Values are expressed as mean(s.d.). Results were computed using BMDP statistical software (BMDP, Los Angeles, California, USA)⁶.

Results

Fifty-two patients older than 64 years underwent elective liver resection. There were 29 women and 23 men, with ages ranging from 65 to 84 (mean 70.4) years. Twenty-two patients had 24 other procedures performed at the time of hepatectomy: resection of a primary colorectal cancer (six patients), biliary drainage (six), partial gastric resection (four), catheterization

of the hepatic artery (three), contralateral liver resection of metastases (two) and cholecystectomy, kidney biopsy and left splenopancreatectomy (one each).

The relation of mortality to age is shown in Table 1. There were 21 major resections (three or more segments removed) with two deaths (10 per cent), both from hepatic failure, and 31 minor resections (fewer than three segments) with one death (3 per cent, P not significant) from cardiac failure. Indications for surgery are listed in Table 2 and the type of resection performed in Table 3. Despite the increasing number of resections performed recently, the mortality rate has been significantly lower since 1982 (no fatality in 34 cases compared with three deaths in 18 patients before 1982, $P = 0.007$). Preoperative ASA grading is presented in Table 4 and did not influence mortality ($P = 0.29$).

Intraoperative blood transfusion was significantly lower in patients who survived surgery (3.0(3.6) units) than in those who died (12.2(3.9) units; $P = 0.008$). Details of fatalities are

Table 1 Age and mortality of 52 patients undergoing elective liver resection

Age group (years)	No. of patients	No. of deaths
65-69	29	1
70-74	12	2
≥ 75	11	0

Table 2 Indications for liver resection

	No. of patients (n = 52)
Malignant tumours	46
Colorectal metastases	24
Other metastases	6
Hepatocarcinoma	8
Other primaries	8
Benign tumours	5
Multiple abscesses	1

given in Table 5. There were no deaths among 24 patients who were transfused 3 units or less. Intraoperative blood requirements have decreased with time (mean 5.4 units before 1982 versus 3.5 units since 1982, $P = 0.075$).

Nineteen patients had at least one complication. Biliary fistulae in three prolonged hospitalization (mean stay of 60 days for these patients versus 19 days for the remaining 49). No reoperation was required for bleeding. One patient required reoperation for a subphrenic abscess after atypical liver resection and right hemicolectomy.

The mean duration of hospital stay after operation was 21 (range 8–74) days. ASA grading and extent of liver resection had no significant influence on the duration of hospital stay (Table 6).

Discussion

Whatever the surgery, postoperative mortality and morbidity rates increase with age; Marx *et al.*⁷ confirmed an increase in mortality rate from 1.0 per cent in patients aged 40 years and younger to 5.1 per cent in patients older than 60 for procedures performed under general anaesthesia. Similarly, only 35 per cent of patients over 64 years of age underwent surgical procedures without any postoperative complications⁸.

Immunological response appears to decrease with age⁹, since sepsis accounted for nearly three-quarters of hospital deaths in

patients older than 64 years undergoing elective hepatectomy for hepatocellular carcinoma, versus one-quarter in younger patients. The overall incidence of hospital death from sepsis was significantly higher in the older patients².

During ageing the liver undergoes physiological changes, such as decrease in size and blood flow (down to 45 per cent)^{10,11}, with alterations in hepatocyte morphology¹². These factors reduce the functional reserve of the organ which may predispose to postoperative liver failure. Fortner and Lincer¹ confirmed the correlation between mortality rate and extent of liver resection in patients aged 64 years or more (4 per cent for left lobectomy versus 31 per cent for extended right hepatectomy).

Factors other than age should be considered in evaluating surgical risk in the elderly. First, conditions such as heart disease, dementia or diabetes have been shown to induce life-threatening complications after operation¹³. Second, postoperative complications in patients aged 65 years and older are significantly lower in patients who were physically active before surgery⁸. Third, ASA grading is known to influence postoperative mortality. This preoperative evaluation may be more significant than age¹⁴. The results for elective liver resection in this series confirm this tendency, although the differences observed were not statistically significant (Tables 4 and 6).

Two other factors have deleterious effects: cirrhosis and intraoperative blood loss. Cirrhosis plays a pejorative role and was responsible for a 30 per cent mortality rate in a series of 23 patients undergoing resection in this centre (unpublished data). Yanaga *et al.*² reported a 52.9 per cent mortality rate in patients older than 64 years with cirrhosis.

Ezaki *et al.*³ suggested that intraoperative blood loss and

Table 3 Resections performed

	No. of patients (<i>n</i> = 52)
Major resection (≥3 segments)	21
Right hepatectomy (V, VI, VII, VIII)	10
Extended right hepatectomy	6
Left hepatectomy (II, III, IV)	4
Other trisegmentectomies	1
Minor resection (<3 segments)	31
Left lobectomy (II, III)	12
Other bisegmentectomies	4
Unisegmentectomy, atypical resections	15

The nomenclature of Couinaud⁵ is followed

Table 4 Mortality and American Society of Anesthesiologists grading

Grade	No. of patients (<i>n</i> = 52)	No. of deaths
I	7	0
II	28	1
III	15	2
IV	2	0

Table 6 Risk factors

	No. of patients	No. of deaths	<i>P</i> †	Mean(s.d.) duration of hospital stay (days)	<i>P</i> ‡
ASA grade					
I and II	35	1	n.s.	20.0(14.1)	n.s.
III and IV	17	2		24.9(16.6)	
Intraoperative blood transfusion (units)					
≤3	24	0	n.s.*	17.0(10.7)	0.04
>3	28	3		25.0(15.6)	
Extent of hepatectomy					
Major	21	2	n.s.	23.2(16.9)	n.s.
Minor	31	1		20.3(14.2)	

* Mean(s.d.) intraoperative blood transfusion was significantly lower in patients who survived (3.0(3.6) units) than in those who died (12.2(3.9) units; $P = 0.008$). ASA, American Society of Anesthesiologists; n.s., not significant; † Fisher's exact two-tailed test; ‡ Student's *t* test

Table 5 Postoperative deaths

Patient		Diagnosis	Procedure	ASA grade	Intraoperative blood transfusion (units)	Cause of death
Age (years)	Sex					
68	F	Metastatic colorectal cancer	Right hepatectomy extended to segment IV	III	10	Liver failure 48 days after operation
73	F	Cancer of gallbladder	Bisegmentectomy (segments IV, V)	III	4	Heart failure 6 days after operation
74	M	Haemangiosarcoma and diffuse liver fibrosis (due to thorium dioxide administration)	Right hepatectomy	II	13	Liver failure 27 days after operation

ASA, American Society of Anesthesiologists

postoperative liver failure were the two critical factors predicting outcome, based on a series of 37 patients aged over 66 years. In the present series, no death occurred in patients with intraoperative transfusions to a maximum of 3 units. Intraoperative blood loss clearly influenced postoperative mortality and duration of hospital stay.

Latterly, blood loss has been minimized using the Pringle manoeuvre, triple clamping and ultrasonic dissection in the vicinity of major vessels. This may explain the better results in the last 34 patients. The three patients who died at the beginning of this series had received multiple transfusions.

In a series of 270 elective liver resections (excluding patients with cirrhosis), the postoperative mortality rate was similar in young and old patients: there were three deaths after 48 resections (6 per cent) in patients aged 64 years and older, compared with seven deaths after 222 resections (3 per cent) in younger patients ($P = 0.39$). The mortality rate did not differ between major and minor resections.

Biliary fistulae, encountered in three patients (6 per cent), considerably prolonged hospitalization time. Chronic cholangitis favours postoperative biliary leakage¹⁵ and was present in one case, while devitalized parenchyma following atypical resection might have caused another biliary fistula. This complication should be reduced with systematic intraoperative cholangiography or methylene blue injection to detect biliary leakage.

Liver resection can be safely undertaken in elderly patients without cirrhosis, provided it is performed on an elective basis. Special attention should be given to minimize intraoperative blood loss.

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Laser resection of a liver hydatid cyst under videolaparoscopy

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Total pericystectomy is the surgical method of choice for hepatic hydatid disease. This was performed under videolaparoscopy using the neodymium yttrium–aluminium–garnet (NdYAG) laser, allowing safe control of all vasculobiliary structures entering the pericyst.

Case report

A 50-year-old north African man in good general condition was admitted in January 1991. He complained of pain in the right upper quadrant of the abdomen, radiating to the right shoulder. He had neither jaundice nor fever. His eating habits included consumption of raw lamb. Blood tests showed a slight eosinophilia with moderate hyperleucocytosis, but results of liver function tests were normal. Abdominal ultrasonography and computed tomography showed a partially calcified mass of the left hepatic lobe, measuring about 6 cm in diameter. The suspected hydatid nature of this mass was confirmed by specific immunological evaluation, particularly the indirect haemagglutination test and immunoelectrophoresis. As this symptomatic hydatid cyst was favourably located at the anterior edge of the left lobe, surgical resection under videolaparoscopy was undertaken. The operation, consisting of total pericystectomy using the NdYAG laser without opening the cyst, lasted for 160 min. The postoperative course was uneventful. Oral fluids were resumed the next day, and a solid diet was started on the second day after operation. The patient left the hospital on the third day after operation and returned to work 1 week after surgery. Histological examination of the cyst confirmed its hydatid nature.

Surgical technique

The procedure uses the plane of cleavage close to the pericyst but outside the adjacent normal friable liver tissue, with step-by-step control of all veins and biliary ducts entering the pericyst (Figure 1).

The patient was prepared with legs apart, the surgeon standing between them. The first assistant or camera assistant stood at the right and the second assistant at the left. Two videomonitors were set on both sides of the anaesthetist to give a good view to the surgeon and the assistants. The patient was surgically draped to allow immediate laparotomy if needed. The pneumoperitoneum was insufflated by puncture of the umbilicus and was electronically controlled at 13 mmHg of constant abdominal pressure. The preoperative monitoring during general anaesthesia included capnography and saturimetry. The straight telescope (0°) attached to a videocamera (Karl Storz, Tuttlingen, Germany) was inserted through a 10-mm trocar and abdominal exploration was performed first. The hydatid cyst was not visible, hidden under inflammatory adhesions. A search for another intra-abdominal localization of the parasite was negative. Three other trocars were then inserted. One 10-mm trocar inserted 5 cm to the left of the umbilicus was to provide an operating channel for endoscopic surgical instruments, such as the electrical hook cannula, scissors, special cannula for the NdYAG laser fibre, and the Endoclip clip applicator (US Surgical, Norwalk, Connecticut, USA). A 5-mm trocar was used for the irrigation–suction tube, and the palpation probe was inserted 2 cm to the left of the xyphoid; the last 5-mm trocar was

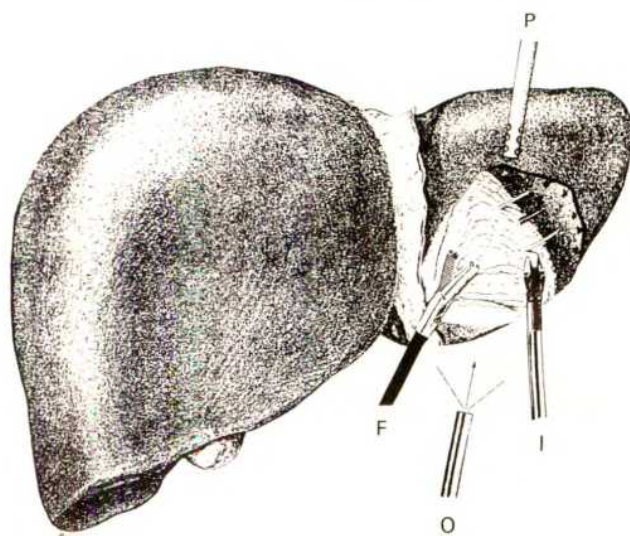


Figure 1 Schematic representation of laparoscopic total pericystectomy and trocar penetration sites. O, 10-mm trocar, straight telescope (0°) and videocamera; F, 5-mm trocar and atraumatic grasping forceps; I, 10-mm trocar and operating channel (for scissors, laser, clip applicator); P, 5-mm trocar and irrigation–suction or palpation probe

reserved for the atraumatic grasping forceps and was inserted symmetrically to the 10-mm operating trocar, 5 cm to the right of the umbilicus (Figure 1).

The surgeon operated using a two-handed technique. After removing the inflammatory peritoneal adhesions with the electrical scissors, the hydatid cyst appeared as a typical white and round homogeneous mass, embedded in the anterior edge of the left lobe. The left lobe was lifted with the irrigation–suction tube and the small adhesions over the cyst were grasped with atraumatic grasping forceps. The liver capsule was then incised using the laser (model 8000; Lasersonics, USA). In this procedure a contact 600-µm silicon fibre without polyethylene tubing was used, coupled with a low-energy helium–neon pilot laser for red targeting. The laser was set at 50 W of power intensity in a continuous-wave mode. The smoke produced during the procedure was regularly suctioned by an irrigation–suction tube placed just behind the cyst. To minimize the risk of haemorrhage, dissection was carried out in a plane of cleavage close to the pericyst, just outside the adjacent normal friable and vascular liver tissue. Any major vasculobiliary elements entering the pericyst were divided between two clips. The minor veins were controlled with the defocused laser beam, allowing a wider and more superficial haemostasis. One useful instrument was the electrical spatula (Karl Storz), which allowed, after flat application on the sectioned liver, direct control of blood oozing. After completion of the dissection and total enucleation of the cyst from the liver, it was inserted into a large sterile rubber condom before extraction. The liver section was checked again, rinsed with saline, and haemostasis was completed using the defocused laser beam. Fibrin sealant, Tissucol (ImmunoCorp, Vienna, Austria), was then applied over the resection area and the two liver edges were pressed together with the help of two closed atraumatic forceps for a short time to ensure compression. Finally, the greater omentum was placed in the residual cavity. No abdominal drainage was needed as haemostasis and biliostasis were considered to be satisfactory. The condom containing the hydatid cyst was then gently extracted from the umbilicus which was widened slightly in a circular fashion to allow easier removal of the specimen. The pneumoperitoneum was then exsufflated and the patient ventilated with a mask to allow better exsufflation. The trocars were finally removed and the small skin incisions closed.

Discussion

The ideal technique for treatment of liver hydatid cysts is total pericystectomy^{1–3} because it allows good visual control of all the biliary ducts and vessels entering the pericyst. It also avoids

opening the cyst and the danger of intra-abdominal contamination by parasitic debris. The partial calcification of the cyst in the present patient helped the surgeon to find the ideal plane of cleavage. During laser dissection, smoke production was less abundant than with monopolar cautery and it was easily cleared by intermittent suction without losing intra-abdominal carbon dioxide pressure. The use of a contact fibre without polyethylene tubing avoided the use of gas to cool the tip of the fibre^{4,5}, which could have led to a dangerous increase in intra-abdominal pressure with a potential risk of gas embolism. An automatic clip applicator was useful in diminishing the number of hand movements. One problem was the extraction of the cyst. In this case, enlargement of the umbilicus allowed the removal of the specimen.

The advantages of laparoscopic surgery are now well known^{6,7}. It is, nevertheless, important to point out that this operation is difficult and should be considered as an advanced laparoscopic procedure of interest to surgeons with previous hepatobiliary, laser and surgical endoscopy experience. When these conditions are met, laparoscopic laser resection of a hydatid cyst may be performed safely. The technique may also be of use for future laparoscopic procedures such as resection of small liver metastases or favourably located small benign tumours.

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Clinical experience with adult polycystic liver disease

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Adult polycystic liver disease is characterized by multiple diffuse cystic lesions of the liver, usually in association with polycystic kidney disease. Rarely, significant liver disease will produce enough symptoms to call for surgical attention. Symptoms range from simple compression to fatal liver failure. Treatment of seven patients (six women) with symptomatic polycystic liver disease over 18 months is reported. Rapidly progressing liver failure and sepsis from infected ascites following puncture developed in one patient and precluded surgery. Another presented with an acute abdomen and anaemia from liver cyst bleeding and was treated conservatively. Five patients with massive hepatomegaly and compression symptoms underwent fenestration and resection to debulk the cystic liver mass. No intra-abdominal drains were used after operation and there were no hospital deaths. One patient developed a bile leak which was managed by percutaneous drainage. Clinical approach, complications and treatment options in adult polycystic liver disease are reviewed.

Adult polycystic liver disease (APLD) is a dominantly inherited disorder of the liver parenchyma. It is characterized by multiple diffuse cystic lesions of the liver, most commonly in association with polycystic kidney disease. An asymptomatic enlarged liver is usually the hallmark of the disease. However, significant symptoms or complications from liver involvement can occur in up to 20 per cent of cases¹⁻³. Timely surgical therapy in such patients may be indicated. We report on seven patients with highly symptomatic APLD. This experience illustrates the broad spectrum of the disease, which can range from mechanical symptoms of compression from liver enlargement to fatal hepatic failure with venous compression and ascites.

Patients and methods

Over an 18-month period seven patients (one man and six women) ranging in age from 34 to 70 years were treated for abdominal symptoms of APLD. Clinical findings are presented in Table 1. Five of the patients had a positive family history of polycystic kidney and liver disease. Four of the six women had had two to four pregnancies. Pulmonary and liver function data are summarized in Table 2. Cerebral computed tomography was performed to rule out an associated cerebral

aneurysm in six of the seven patients⁴⁻⁶. Consultation with other family members and genetic counselling were offered to all six patients considered for operation.

The only man in the series had end-stage renal failure secondary to adult polycystic kidney disease. He presented acutely with abdominal pain, hypotension and a fall in haemoglobin concentration. Because of his age, and because he was not considered a candidate for operation, he was investigated less extensively than the other six patients.

Treatment

Surgical treatment was offered to patients 1-6 with compression symptoms (Table 1). Patients 1-5 underwent fenestration and resection^{6,7} (Table 3). Patient 6 had severe mechanical complications with inferior vena cava compression (Figure 1) from massive hepatomegaly (Figure 2). She initially refused fenestration and resection and went to another hospital where she was treated by repeated tapping of ascites. This patient presented again as an emergency but because of advanced liver failure and infected ascites was unsuitable for operation. To try to improve a deteriorating clinical condition, extensive ultrasonographically guided cyst puncture was performed. Although this seemed to relieve some of the vascular compression,

Table 1 Clinical findings and extent of disease

Patient no.	Age (years)	Sex	Symptoms	Clinical findings	Involved organs
1	41	F	Abdominal pain Orthopnoea	Massive hepatomegaly Bilateral elevated diaphragm Leg oedema	Polycystic liver and kidney Mesenteric cyst
2	46	F	Abdominal pressure Dyspnoea Early satiety	Massive hepatomegaly Haemorrhoids	Polycystic liver
3	34	F	Abdominal distension and pressure Early satiety	Massive hepatomegaly Palpable left kidney Bilateral elevated diaphragm	Polycystic liver and kidney
4	40	F	Abdominal pressure Early satiety	Massive hepatomegaly	Polycystic liver and kidney
5	37	F	Abdominal distension and pressure	Massive hepatomegaly	Polycystic liver and kidney
6	56	F	Abdominal distension and pressure Dyspnoea	Massive hepatomegaly Subcutaneous collateral venous circulation Ascites, flapping tremor, jaundice	Polycystic liver and kidney Polycystic pancreas
7	70	M	Sudden diffuse abdominal pain	Hepatosplenomegaly Portal hypertension	Polycystic liver and kidney

Table 2 Lung function and laboratory data

	Normal range	Patient no.						
		1	2	3	4	5	6	7
Lung function								
Vital capacity (ml)		<u>3580</u> (3940)	3980 (3640)	—	5580 (4620)	—	<u>2130</u> (4100)	—
FEV ₁ (ml)		2685	3223	—	<u>4073</u>	—	1780	—
Laboratory data								
Aspartate aminotransferase (units l ⁻¹)	11–36	15	35	29	25	30	<u>434</u>	13
Alanine aminotransferase (units l ⁻¹)	10–41	14	<u>49</u>	26	30	18	<u>394</u>	7
Bilirubin (μmol l ⁻¹)	3.4–25.7	14	7	8	9	11	<u>174</u>	14
Alkaline phosphatase (units l ⁻¹)	36–120	85	<u>164</u>	75	49	97	<u>1070</u>	101
Albumin (g l ⁻¹)	30.0–50.0	39.2	42.0	39.6	39.3	38.0	30.2	34.0
Prothrombin time (%)	70–130	94	95	96	78	<u>59</u>	<u>43</u>	<u>48</u>
Creatinine (μmol l ⁻¹)	45–102	81	91	89	112	76	121	676
Creatinine clearance (ml min ⁻¹ 0.57 m ⁻²)	75–127	96	—	80	<u>63.9</u>	—	47	Haemodialysis
Amylase (units l ⁻¹)	63–228							
Before operation		163	217	94	122	92	144	129
After operation		<u>802</u>	111	292	<u>966</u>	—	—	—

Values in parentheses are normal for patient; abnormal values are underlined. FEV₁, forced expiratory volume in 1 s (normal value ≥75 per cent of vital capacity)

Table 3 Operative data, length of stay and complications

Patient no.	Extent of resection (segments)	Perioperative transfusion (units)	Hospital stay (days)	Complications
1	II, V, VI, VII, VIII	4	24	Ascites and right pleural effusion Generalized oedema Pancreatitis
2	II, III, IV	0	16	Ascites and right pleural effusion Cholestasis
3	I, III, IV, VII, VIII	4	24	Ascites, bile leak
4	IV, V, VIII	12	15	Ascites and right pleural effusion Wound seroma
5	IV, V, VI	2	22	Ascites and fever

patient 6 died from hepatorenal failure secondary to overwhelming sepsis.

Patient 7, with suspicion of bleeding, underwent computed tomography (CT) which was not diagnostic; magnetic resonance imaging revealed acute and subacute bleeding in liver cysts (*Figure 3*). He was successfully treated with transfusions and fresh frozen plasma. Embolization was not necessary.

Surgical technique

CT of patients before operation allowed definition of the cystic areas to be resected. In all patients a solid parenchymatous area not replaced by cysts was defined and the replaced cystic lobe(s) and/or segment(s) were noted. Through a bilateral subcostal incision the lobe(s) and/or segment(s) of totally replaced parenchyma were primarily resected. Transhepatic fenestration then allowed intraoperative assessment of the extent of liver that could be further resected. The procedure included cholecystectomy in all five patients. Portal branches, arteries, sectoral ducts and hepatic veins are distorted by liver cysts. These major structures supplying residual parenchyma were preserved. As many residual smaller cysts as possible were deroofed. The appearance of the liver surface before and after operation is shown in *Figure 4* (patient 3). After resection the exposed edges of cysts were coagulated or suture ligated if necessary. Any obvious bile leak was oversewn. Fibrin glue (Tissucol; Immuno, Vienna, Austria) was used over large areas of



Figure 1 Significant inferior vena cava compression from polycystic liver with paravertebral collateral venous drainage (patient 6)

unsealed liver tissue. In all five patients, the abdomen was closed without drainage to restrict fluid losses.

Results

Treatment after operation included the H₂-receptor blocker ranitidine and long-acting somatostatin (octreotide (Sandostatine); Sandoz, Basel, Switzerland) to minimize development of ascites through the surface of the exposed cyst remnants. All patients were maintained on octreotide and ranitidine until the ascites had disappeared. Albumin levels were maintained in the

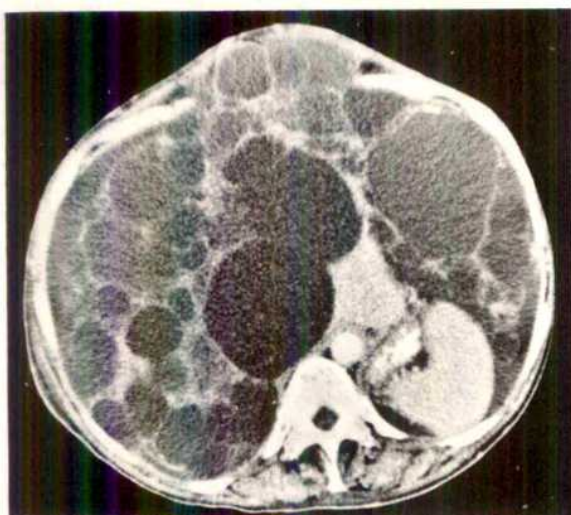


Figure 2 Massive polycystic hepatomegaly resulting in restrictive lung function (patient 6)

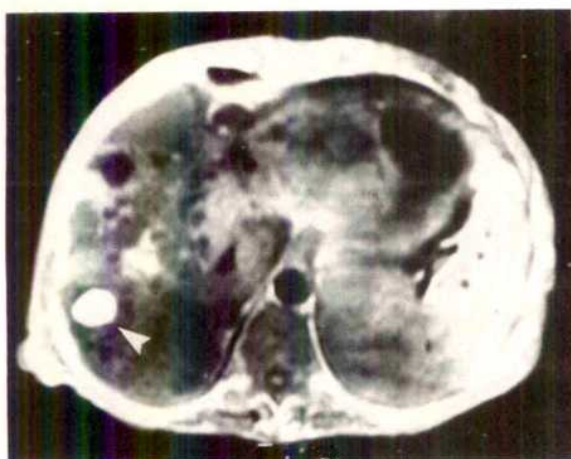
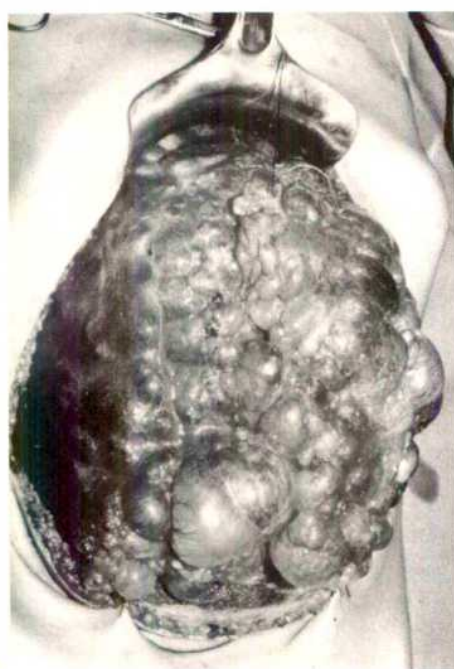


Figure 3 T1 phase of magnetic resonance imaging confirms acute bleeding (arrow) which was not demonstrated by computed tomography (patient 7)



a



b

Figure 4 Appearance of the liver at **a** the start and **b** the conclusion of the fenestration and resection operation (patient 3)

normal range by intravenous supplementation. Development of ascites was further treated by fluid restriction and diuretics as necessary.

Complications and length of hospital stay are summarized in Table 3. All five patients developed ascites; this was successfully managed conservatively in all cases. In patient 3 a raised serum bilirubin concentration with a normal alkaline phosphatase level led to a diagnostic puncture of the abdomen in which bile-stained ascitic fluid was found. This bile leak was managed by ultrasonographically guided percutaneous drainage. The drain was removed after 6 days without further complication. Significant elevation of serum amylase concentration occurred in patients 1 and 4, with symptoms consistent with pancreatitis in patient 1.

Follow-up with this preliminary experience is short, a mean (s.d.) of 14 (7) (range 6–27) months, but the technique of fenestration and resection, besides its obvious cosmetic benefit, has provided complete relief of compression symptoms in all five patients.

Discussion

APLD, first described by Bristowe in association with polycystic kidney disease⁸, is a dominantly inherited condition that rarely presents to the surgeon because it remains largely asymptomatic. The age and sex distribution of the population studied determines the association between APLD and polycystic kidney disease^{9,10}. While up to 93 per cent of patients with APLD have associated kidney disease^{4,10}, systematic studies have shown that 34–78 per cent of patients with polycystic kidney disease have cystic livers^{5,10–13}. All but one patient in this series had polycystic kidney disease. Other organs can be involved in 1–3 per cent of cases^{2,14} and this occurred in two of the patients presented, one having a polycystic pancreas and the other a mesenteric cyst.

APLD is a rare disorder. Kwok and Lewin⁴ reported an autopsy prevalence of 0.13 per cent in 1988 compared with an earlier report¹⁵ of 0.03 per cent in 1959. An increased prevalence is found in women, with the number of cysts correlating with the number of pregnancies¹⁶. In the present group of patients only one of the five women had not had a previous pregnancy. The disease manifests between 40 and 60 years of age and symptoms include abdominal swelling, intermittent attacks of pain, pain on stooping, and dyspnoea in 20 per cent of patients².

Acute complications are more frequently associated with renal cysts than hepatic cysts, and the prognosis of APLD is usually determined by the prognosis of the kidney disease. However, according to Grünfeld *et al.*³ more than 10 per cent of deaths in patients with APLD occur following liver complications. While most large series have reported a slight elevation of serum alkaline phosphatase level^{2,17}, frank jaundice or portal hypertension with varices occur very rarely as true complications of cyst compression¹. Septic complications of ascites or hepatic cysts are devastating and can lead to liver failure and death¹⁸. In patient 6 *Escherichia coli* and streptococcal peritonitis with liver decompensation prevented further therapy. The ¹¹¹In-radiolabelled leucocyte scan has been used to localize infected cysts¹⁹. Acute abdominal pain associated with a fall in haemoglobin level suggests the diagnosis of bleeding into a cyst. While CT accurately delineates the anatomy of APLD, magnetic resonance imaging is superior in confirming bleeding²⁰.

The treatment of APLD remains controversial, ranging from cyst puncture to combined liver and kidney transplantation²¹⁻²³. The timing of surgery is also controversial. Clinical judgement should dictate the treatment. The vast majority of patients require reassurance, family assistance and, if necessary, genetic counselling because prenatal diagnosis is now possible¹. In APLD, cyst aspiration and sclerosis²¹ apply only to the occasional patient whose symptoms can be clearly attributed to compression from a single large cyst. Likewise, laparoscopic deroofing, recently described for solitary cysts²⁴, cannot be proposed for patients with a multitude of cysts extending from xyphoid to pubis.

The technique of transhepatic fenestration described by Lin *et al.*²⁵ in 1968 has been used in symptomatic patients. Recurrence has been reported²⁶. In a series of nine patients in whom transhepatic fenestration was used, van Erpecum *et al.*¹⁷ reported symptomatic relief but no change in liver size. We believe fenestration should be coupled with resection. Initial experience with fenestration and resection was complicated by a difficult period after operation because of fluid losses or haemorrhage^{7,27}. Secretin has been shown to influence biliary secretion²⁸ and could, therefore, probably modify the epithelial secretion of the cysts. Huguet *et al.*²⁷ have shown reduction of cyst secretion using cimetidine. We have used secretin inhibitors such as long-acting somatostatin and H₂-blockers in all patients. The beneficial effect of somatostatin was demonstrated by the apparent control of ascites, but proof of the efficacy of somatostatin by comparison with untreated patients cannot be provided. Fluid losses were considerably reduced by the omission of drainage. Clinical surveillance allowed prompt detection of a bile leak in patient 3 and percutaneous puncture allowed adequate drainage. Pleural effusions, which are also common, should be carefully monitored. Diagnostic puncture can be used in cases of fever of uncertain aetiology after operation.

Long-term results of fenestration and resection are still awaited. Patients with APLD tend to accommodate to their disease and minimize their symptoms. Recently, Newman *et al.*⁶ have also shown satisfactory cosmetic and symptomatic relief with fenestration and resection. In carefully selected patients operation should be proposed early before the development of advanced APLD, which is associated with cachexia, liver failure and respiratory insufficiency. In such cases combined liver and kidney transplantation remains the last resort²³.

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Case report

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Partial autotransplantation of the liver in hepatocellular carcinoma complicating cirrhosis

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The first requisite for success in hepatic resection is sufficient functional reserve of the residual liver. While the normal liver allows removal of more than 70 per cent of the total hepatic volume, the extent of safe resection in the cirrhotic organ is far less¹, thereby limiting the scope of surgery for concomitant hepatoma^{2,3}.

A case is presented of hepatic malignancy in a cirrhotic patient in whom conventional removal would have entailed resection of the left liver plus the caudate lobe, amounting to approximately 60 per cent of the total hepatic volume⁴. The patient's limited hepatic functional reserve made such a major resection too risky⁵. The problem was tackled by restoring much of the tumour-free tissue to the patient after bench removal of the hepatoma.

Case report

A 58-year-old woman was admitted with hepatocellular carcinoma. She had a 10-year history of hypertension and chronic hepatitis (positive for hepatitis C virus antibody). Computed tomography (CT) and magnetic resonance imaging (Figure 1) showed a tumour 5.8 × 4.6 cm in size located in segment IV and extending into segments II, III and I. Assessment by CT indicated that the whole liver volume

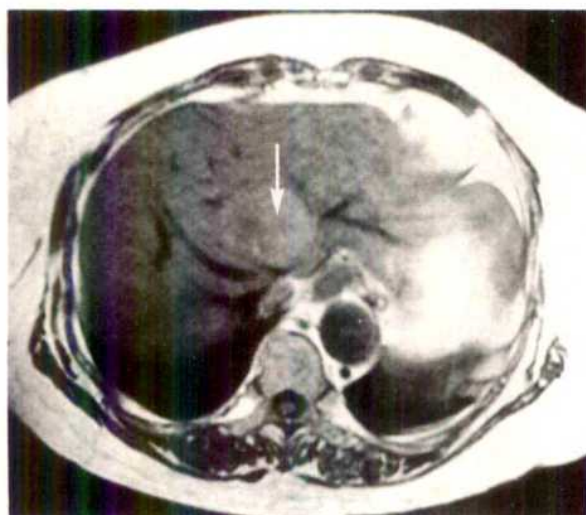


Figure 1 Magnetic resonance image showing the tumour (arrowed) in segment IV of the liver

was 1156.4 cm³, with segments V, VI, VII and VIII comprising 492.5 cm³, segments II and III 514.5 cm³, segment I 19.2 cm³ and the tumour 92.4 cm³. Investigations showed liver cirrhosis, splenomegaly, pleural effusion and an arterial supply to the right liver from the superior mesenteric artery.

Oesophageal varices were not seen on endoscopy, although varices of the left gastric vein were demonstrated by portography. Investigation showed a decreased platelet count (96×10^9 /litre), low serum albumin level (37 g/l), slightly raised total bilirubin level (22.2 µmol/l) and a diabetic pattern on glucose tolerance test. Doppler flowmetry of the portal vein suggested a cirrhotic pattern (flow volume 380 l/min, velocity 9 cm/s). Redox tolerance index⁵ was 0.47.

The operative procedure is shown in Figure 2. Laparotomy revealed slight ascites and a nodular liver with a pale and apparently atrophic right lobe. Intraoperative ultrasonography confirmed that the tumour was thickly encapsulated and widely adherent to the confluence of the left and middle hepatic veins. The hepatic parenchyma was meticulously divided along Cantlie's line without interruption of the hilar vessels, with blood loss of less than 1 litre during isolation of segments II, III and IV and removal of segment I. Segments II, III and IV were totally isolated from the adjacent tissues and were perfused through the portal tract with 250 ml Ringer's lactate solution containing 10 mg heparin, followed by 500 ml University of Wisconsin solution (each chilled to 4°C) before removal to the bench. The tumour was dissected from the left hepatic vein wall, and some points of adherence or infiltration were resected, together with most of segment IV, which surrounded the lesion. The hepatic vein was repaired at the sites of damage including the orifice of the middle hepatic vein. Segment I was also resected. Segments II, III and a part of segment IV were then replaced in the patient at the original site. The preservative solution was washed out with normothermic Ringer's lactate. Reanastomosis of the hepatic and portal veins, followed by the hepatic artery, was performed. Operating

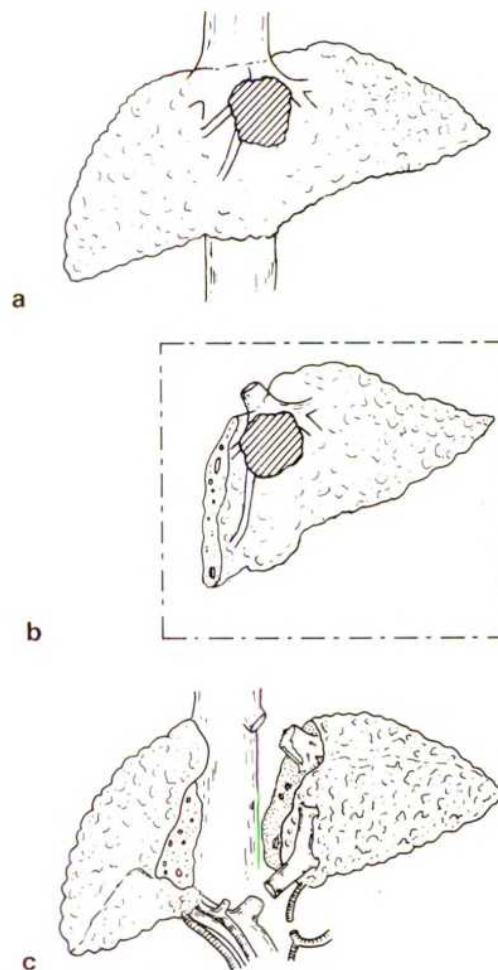


Figure 2 Operative procedures used: a resection; b back-table procedure; c reanastomosis. The cross-hatched area represents the tumour

time was 100 min on the bench and 38 min for reconstruction of both the hepatic and portal veins. Bile duct reconstruction was performed by a Roux-en-Y procedure and bile excretion was observed through a transhepatic tube in the reconstructed bile duct. Perioperative assessment of the arterial ketone body ratio (AKBR)^{6,7} showed a value between 0.7 and 1.0 during the bench procedure, and 1.31 immediately after portal flow was re-established. After arterial reperfusion, the AKBR promptly increased to 2.46. Histological examination of the liver parenchyma revealed widespread pseudolobules with diffuse fibrosis and interstitial infiltrates of lymphocytes.

The postoperative course was uneventful apart from persistent drainage of a pleural effusion for 7 days. The maximal values of glutamic oxaloacetic transaminase (264 units/l) and lactic dehydrogenase (741 units/l) were reached on the third day and returned to normal by 10 days; likewise serum bilirubin (102.6 μ mol/l on the eighth day) was normal at 3 weeks. Doppler flowmetry of the left portal vein revealed a flow volume of 220 ml/min on the second day and more than 600 ml/min on the 22nd day. The transhepatic bile duct catheter was removed on the 25th day. The patient was discharged from the surgical ward 4 weeks after the operation. Repeat imaging was normal at 7 months and the patient remains well at 11 months.

Discussion

Resection of segments I, II, III and IV, which was necessary for extirpation of the tumour, was thought likely to cause critical impairment of liver function in this cirrhotic patient.

Assessment of hepatic volume by CT indicated that segments V, VI, VII and VIII occupied only about 40 per cent of the whole liver. An index of less than 0.5 on redox tolerance test predicts a high incidence of complications and death after major liver resection. Other hazards in resecting cirrhotic livers include the large operative blood loss and prolonged hepatic vascular exclusion^{8,9}. Thus, in this patient, resection of segment IV accompanied by conventional *in situ* dissection of the tumour from the left hepatic vein was considered to be too risky. Extracorporeal surgery presented an alternative in this situation¹⁰. In this type of operation, however, and especially in cirrhosis, one cannot know in advance whether the retransplanted liver will be able to clear the metabolic load accumulated during the period of cold ischaemic injury.

The rapid restoration of AKBR⁷ after autotransplantation of segments II and III in the present patient is attributable to the contribution of the right liver in reducing the metabolic load before the retransplanted segments of the left lobe resumed their function. Although AKBR values of 0.7–1.0 would

normally predict a high morbidity and mortality rate after resection of the left liver⁶, retention of AKBR above 0.7 during the period of bench dissection indicated that segments V, VI, VII and VIII were able to clear the metabolic load, at least in part, during this critical phase. The extracorporeal procedure was therefore based on the concept that the maintenance of a high level of hepatic energy is fundamental to successful liver surgery¹¹.

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Case report

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Successful treatment of complete inferior vena cava thrombosis after liver transplantation by thrombolytic therapy

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Complete inferior vena cava (IVC) thrombosis after orthotopic liver transplantation (OLT) is a rare and usually lethal complication reported mainly in children. A case of complete IVC, hepatic and renal vein thrombosis after OLT is reported. Caval thrombosis was successfully treated by high-dose intracaval urokinase thrombolysis.

Case report

An urgent OLT was performed in a 51-year-old woman for fulminant liver failure, probably due to non-A-non-B hepatitis. Postoperative liver function was excellent; however, 4 weeks later, large pleural and peritoneal effusions developed with gross oedema of the abdominal

wall and lower extremities and with persistent severe systolic hypotension. Renal function deteriorated, requiring haemodialysis, and liver function became impaired.

Transfemoral inferior cavography showed a complete IVC thrombosis involving both renal veins. The iliac and femoral veins were patent (Figure 1). A catheter was advanced through the thrombosed IVC segment, and selective hepatic phlebography showed thrombotic occlusion of the right vein but a patent left vein. Coeliac angiography demonstrated patent hepatic arteries and free portal venous drainage. No narrowing of the anastomoses was noted.

Intracaval thrombolytic therapy was started, beginning with intrathrombotic application of 500 000 units urokinase within 2 h, followed by a continuous intracaval infusion of 125 000 units/h over 72 h. A cumulative dose of 9 500 000 units urokinase was administered. Systemic anticoagulation involved intravenous heparin in a dose of 35 000 units/day.

Cavography after 3 days revealed patent renal veins, and disappearance of all thrombotic material in the suprarenal vena cava. Residual thrombus was detected in the infrarenal segment (Figure 2). Complete lysis could be demonstrated 2 days later. Effective thrombolysis was followed by general stabilization of the clinical situation. The patient was discharged from hospital 4 weeks later with no further complications, and 10 months after the incident remains well under warfarin medication.

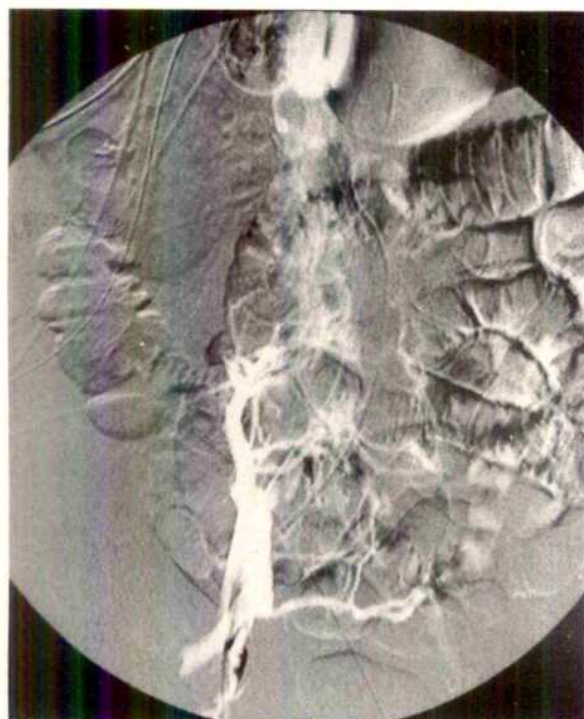


Figure 1 Transfemoral cavography (digital subtraction angiography technique) showing an early phase of complete inferior vena cava thrombosis with patency of the right iliac and femoral veins. Collateral circulation has not been fully developed at this stage. Intestinal radiographic artefacts are visible in the upper median part of the picture

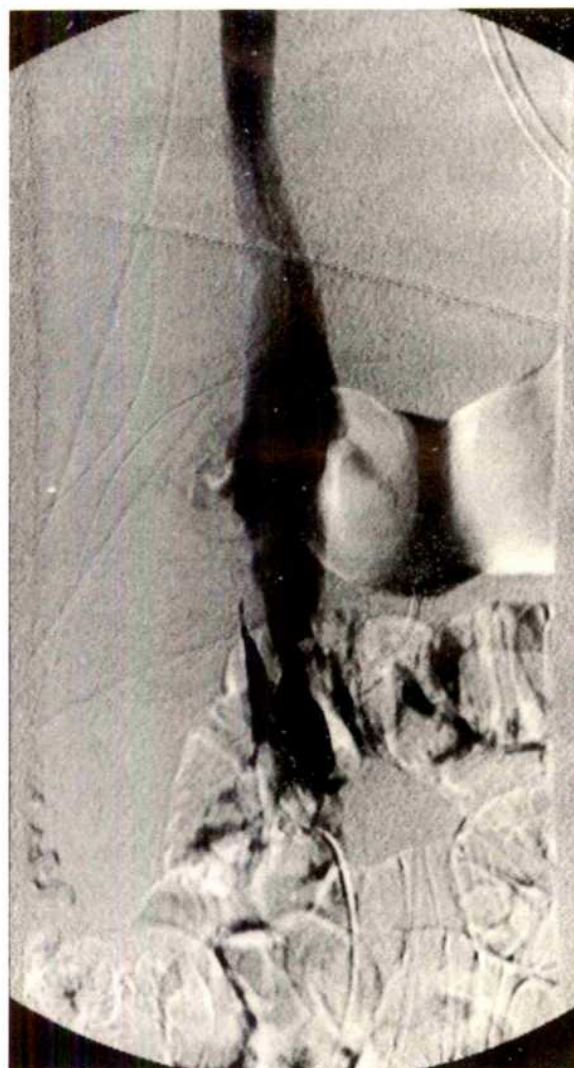


Figure 2 Transfemoral cavography showing successful thrombolysis of inferior vena cava (IVC) thrombosis after 3 days of intrathrombotic urokinase infusion. Residual thrombotic material is detected only in the lower parts of the IVC. Complete lysis of all caval and hepatic segments was demonstrated 2 days later

Discussion

IVC thrombosis after OLT is a rare and usually lethal event. Despite previous pessimism concerning grafting of the portal vein or the IVC (based on experimental data), venous thrombotic complications do not pose a major problem in adult liver transplantation^{1,2}. The complex aetiology of IVC thrombosis in general is well documented³, but it is thought to be a secondary phenomenon in most patients undergoing transplantation. It is frequently confined to the lower infrarenal segment of cava outside the operative site, as the increase in caval blood flow at the level of the renal veins probably limits upward extension³.

Caval suture lines after OLT possibly serve as a nidus for thrombus formation, particularly in the case of caval strictures, endothelial flaps or lesions. Literature review suggests that in contrast to vessels of smaller diameter, slight technical errors at both suprahepatic or infrahepatic caval anastomoses during OLT are of minor importance for local thrombotic complications in adults. Consequently, IVC thrombosis has been reported mainly after paediatric liver transplantation^{1,2}.

The pathogenesis of IVC thrombosis in this case remains speculative. The most common cause in all surgical patients is extension of thrombus from the deep femoral and iliac veins, which was not detected in this patient. Hypercoagulable states are seldom found in the early aftermath of OLT, particularly if liver function is satisfactory.

As complete caval thrombosis after OLT is usually fatal, and surgical thrombectomy is rarely feasible in such a critical situation⁴, controlled but aggressive enzymatic thrombolysis should be attempted as an ultimate rescue treatment. Various case reports have documented the potential effectiveness of such an approach, so far performed mostly for superior vena caval thrombosis⁵. This is the first report of successful enzymatic thrombolysis of IVC thrombosis plus renal and hepatic vein thrombosis after a major operation such as OLT.

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Case report

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Strangulated small bowel hernia of the falciform ligament

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Small bowel obstruction with subsequent strangulation occurs most commonly as a result of intra-abdominal adhesions or in external hernias. Internal hernias into the peritoneal fossae, the foramen of Winslow, and anomalous openings in the mesentery, broad ligament and omentum account for fewer than 1 per cent of all such hernias¹. An unusual case of a strangulated small bowel hernia of the falciform ligament is reported.

Case report

A 34-year-old man presented with a 5-h history of severe colicky epigastric pain, with vomiting of copious quantities of partially digested food. There was no similar previous episode and no history of surgery. Physical examination revealed abdominal distension with tenderness in the epigastrium. There were no external hernias. Bowel sounds were obstructive but the patient was afebrile and normotensive.

A nasogastric tube was passed before performing a plain abdominal radiograph, which showed multiple dilated loops of small bowel. Erect chest radiography revealed what appeared to be free air under both hemidiaphragms (Figure 1). The radiological features confirmed the clinical impression of small bowel obstruction with possible perforation. Urgent laparotomy was performed, revealing a 30-cm loop of infarcted small intestine in the left upper quadrant. There was no evidence of free perforation. The loop of mid-small bowel had herniated from right to left through a 3-cm defect in the falciform ligament, coming to lie under the left hemidiaphragm. Air within the lumen of the loop had given the impression of free air under the diaphragm.

The falciform ligament was divided and the infarcted segment of small bowel resected. A primary anastomosis of small bowel was performed. The patient made a rapid and uneventful postoperative recovery.

Discussion

Herniation of intra-abdominal contents through a defect in the falciform ligament is an uncommon occurrence, with fewer than ten cases reported since it was first described by Blunt and Rich² in 1968. Such hernias commonly contain small bowel, although herniation of greater omentum and the entire right hemicolon has been recorded³. The defect in the falciform

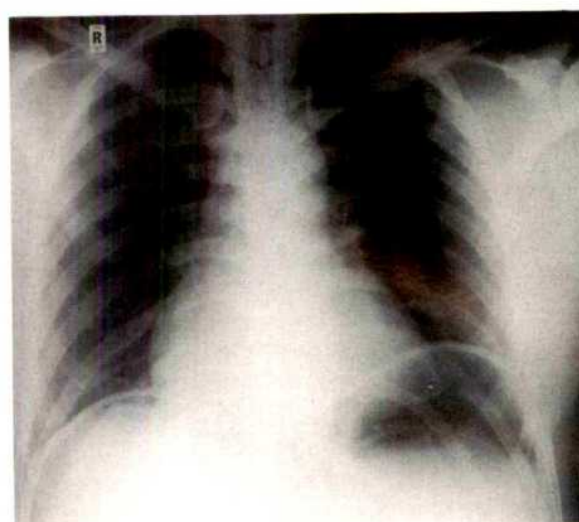


Figure 1 Erect chest radiograph giving the impression of free air under the left and right hemidiaphragms

ligament appears to be congenital as herniation has been reported not only in a newborn infant⁴, but Svendsen *et al.*⁵ have described a case of herniation following complete failure of development of the falciform ligament itself, leaving only the ligamentum teres (obliterated left umbilical vein) as a long intraperitoneal band extending from the umbilicus to the liver.

Although uncommon, this case highlights the importance of internal herniation as a cause of acute small bowel obstruction, especially in patients with no evidence of external hernia and no previous surgery. These hernias may contain a closed loop, are unlikely to reduce spontaneously, and commonly progress to strangulation. In such cases prompt surgical intervention is required to prevent the development of infarction.

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Meconium ileus: a review 1972-1990

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Recent reports from North America have shown decreasing mortality rates in neonates with meconium ileus. This study was undertaken to review the management and mortality of neonates with meconium ileus who presented to a paediatric surgical unit in the west of Scotland from 1972 to 1990.

Patients and methods

All patients with a diagnosis of meconium ileus and cystic fibrosis who were treated in one paediatric surgical unit from 1972 to 1990 inclusive were identified and their case notes reviewed. All patients had a positive sweat test or diagnostic appearances on histology of resected specimens or autopsy specimens if death occurred before a sweat test had been performed. Patients were categorized as simple, with inspissated meconium in the ileum with dilated loops proximally, or complicated, with volvulus or atresia and/or a perforation resulting in meconium peritonitis.

Results

A total of 53 patients with meconium ileus and cystic fibrosis was treated from 1972 to 1990. Of these, 44 had simple and nine complicated meconium ileus. From 1972 to 1980, 15 patients presented; 38 presented from 1981 to 1990. The clinical presentation always included abdominal distension; bilious vomiting also occurred in almost 45 per cent of patients in both groups. Eight patients (15 per cent) had a family history of cystic fibrosis.

Simple meconium ileus

There were 21 female and 23 male patients with simple meconium ileus. The mean gestational age was 39 weeks and they had a mean birth-weight of 2.97 kg. Only one patient in the simple group had a significant prenatal event. In this patient prenatal ultrasonography had shown an intra-abdominal mass which turned out to be meconium-laden loops of bowel. The mean age at transfer to the surgical centre was 51 h.

Gastrografin enema. Forty patients with simple meconium ileus underwent at least one Gastrografin enema (Schering Health Care, Burgess Hill, UK) treatment. Of these patients 26 were successfully relieved of obstruction by the enema alone. The number of enemas required to relieve the obstruction in these 26 patients is shown in Figure 1.

Half of the patients were successfully treated with either one or two enemas and 77 per cent by up to four enemas. One patient required a total of seven enemas. A total of 80 enemas was administered to 40 patients with simple meconium ileus and four perforations occurred, giving a perforation rate of 5 per cent. One perforation occurred after the initial Gastrografin enema and the other three occurred after or during the second enema. Of these four patients with perforations, two

This article reviews the management and mortality of 53 neonates with meconium ileus and cystic fibrosis treated in one paediatric surgical centre from 1972 to 1990. Forty-four patients (83 per cent) presented with simple meconium ileus and 26 of 40 patients in this group were successfully treated with Gastrografin enemas. Four patients suffered a perforation as a result of the enema (perforation rate 5 per cent). The 1-year survival rate for simple meconium ileus was 81 per cent and for complicated meconium ileus 75 per cent.

underwent surgery and survived, one underwent surgery and died and the fourth patient died from an unrecognized perforation without undergoing surgery.

Surgery. Four patients with simple meconium ileus did not receive a Gastrografin enema and went straight to emergency surgery with a mistaken preoperative diagnosis of volvulus or atresia on clinical and plain radiological findings. Thirteen other patients with simple meconium ileus who had unsuccessfully undergone Gastrografin enema treatment or had suffered a perforation also underwent surgery. Ten patients underwent small bowel resection or enterotomy and formation of a Bishop-Koop (seven patients) or Santulli (three patients) ileostomy. Four patients underwent resection and exteriorization of the bowel ends. Enterotomy and intraoperative irrigation was successful in two patients and only one underwent resection and primary anastomosis. The immediate surgical complications were two leaks from Bishop-Koop or Santulli ileostomies and necrosis of one stoma. All three patients required relaparotomy: one patient with a leak survived and the other two died.

Complicated meconium ileus

There were five female and four male patients with complicated meconium ileus. Their mean gestational age was 37.5 weeks and mean birth-weight was 3.27 kg. Two patients had associated polyhydramnios giving rise to early labour. In two patients a prenatal diagnosis of intestinal obstruction was made, which led to induction of labour before term. The complications in this group comprised: volvulus (two patients), giant cystic meconium peritonitis (two patients) and perforation with meconium peritonitis (five patients). Three patients underwent initial Gastrografin enema treatment as it was not obvious from plain abdominal radiography that a complication was present. Eight of the nine patients then underwent emergency bowel

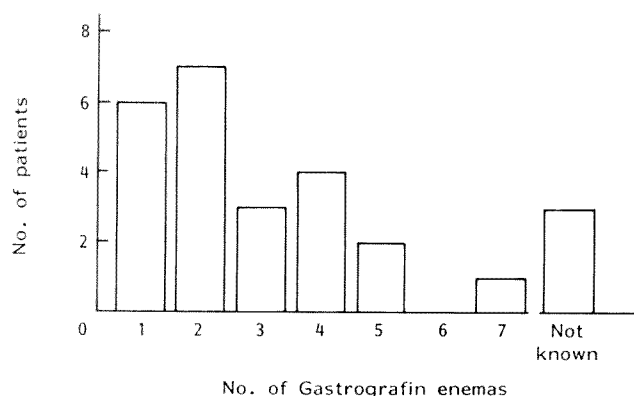


Figure 1 Number of enemas required to relieve the obstruction in 26 neonates with simple meconium ileus successfully treated with Gastrografin enemas alone

Preliminary work presented to the Scottish Surgical Paediatric Society in Edinburgh, November 1990 and published in abstract form as Scott Med J 1991; 36; 94

Table 1 Overall and operative mortality rates in neonates with simple meconium ileus, with breakdown for the periods 1972–1980 and 1981–1990

Period	Overall mortality rate	Operative mortality rate
1972–1990	5 of 44 (11)	3 of 17 (18)
1972–1980	1 of 12 (8)	0 of 3
1981–1990	4 of 32 (12)	3 of 14 (21)

Values in parentheses are percentages

resection and formation of double stomas. The ninth patient who had disseminated intravascular coagulation and fulminating sepsis underwent simple tube drainage of the abdomen in an attempt to improve his condition before surgery.

Mortality

The 30-day mortality rate for simple meconium ileus was 11 per cent (five patients). The overall and operative mortality rates for patients with simple meconium ileus, with a breakdown into the two decades of the study, are shown in Table 1. The 30-day mortality rate for complicated meconium ileus was 22 per cent (two patients, one in each decade). All the deaths were related to sepsis (four abdominal sepsis, two septicaemia and one pneumonia). Hence the overall 30-day mortality rate for patients presenting with meconium ileus in this series was 13 per cent. In patients followed for 1 year, the survival rate was 81 per cent (34 of 42) and 75 per cent (six of eight) for simple and complicated meconium ileus respectively. Of the seven deaths occurring in the first month of life, six patients were male.

Discussion

Meconium ileus is an intraluminal intestinal obstruction first described by Landsteiner in 1905¹. The vast majority of patients with this condition have cystic fibrosis, as first noted by Andersen² in 1938, although there have been occasional reports to the contrary^{3,4}. Meconium ileus is the initial presentation in 10–15 per cent of all patients with cystic fibrosis⁵.

Meconium ileus can be either simple or complicated. The usual complications are intrauterine volvulus, atresia, perforation/meconium peritonitis or giant cystic meconium peritonitis⁶. Before 1969 meconium ileus was managed operatively⁷ with a high mortality rate, but since Noblett's report of the use of Gastrografin enemas in the treatment of simple meconium ileus⁸, non-operative management has taken an increasingly important role. With this non-operative treatment and advances in neonatal anaesthesia and intensive care the mortality rate has decreased dramatically from greater than 60 per cent in 1940–1965⁷ to 0–15 per cent recently^{9,10}.

Of the 53 patients in this study, 83 per cent had simple meconium ileus, a substantially higher proportion than in previous reports^{9–13}. The mean gestational age in the simple group was slightly higher than that in the complicated group. This is consistent with an increased incidence of prenatal events leading to earlier delivery in the complicated group. Only eight patients (15 per cent) had a family history of cystic fibrosis, similar to values in other reports of 10–14 per cent^{9,11–13}.

Gastrografin enemas were successful in relieving the obstruction in 59 per cent of patients with simple meconium ileus, a number similar to that in other reported series^{11–13}. The policy at this hospital has been to perform repeated Gastrografin enema administration as long as the infant remains well¹⁴. The perforation rate of 5 per cent in this series is lower than the figures of 11 and 15 per cent reported previously^{11,13}. Although the perforation rate in this series was only 5 per cent, the mortality rate for patients suffering a perforation was 50 per cent. No patient showed evidence of circulatory collapse either during or after the Gastrografin

enema owing to the theoretical possibility of hypovolaemia¹⁵ and no patient suffered intestinal necrosis¹⁶.

Other authors have stated that surgery for simple meconium ileus should be limited to enterotomy and intraoperative irrigation¹⁰ or resection and primary anastomosis^{9,10}. Results in this series support this policy, as a 20 per cent rate of leakage was found in Bishop–Koop or Santulli ileostomies. These types of defunctioning ileostomy were useful as a safe means of starting enteral fluid replacement and nutrition early in the postoperative period, with a safety valve arrangement, before complete distal bowel function was regained¹⁷. The need for enteral fluid replacement is now less important, and therefore in simple meconium ileus we would advocate enterotomy and intraoperative irrigation, with either *N*-acetylcysteine¹⁰ or Gastrografin¹³, or resection and primary anastomosis. In complicated meconium ileus, Gastrografin enema has no therapeutic role and surgery is the only available treatment. Resection and formation of a double stoma is usually appropriate as the neonate is likely to be in a very poor general condition and the abdomen is usually grossly contaminated with meconium.

The overall 30-day mortality rate in this series was 13 per cent. Caniano and Beaver reported nil 30-day mortality in 42 patients with meconium ileus¹¹, but their patients were transferred to the surgical centre earlier than those in this series. There may also be differences in neonatal intensive care between Scotland and North America. It is surprising that the mortality rate for neonates with simple meconium ileus has not changed over the two decades of this study (8 per cent for 1972–1980 and 12 per cent for 1981–1990). Of our seven deaths six were in male patients. This male preponderance in mortality has not been noted previously for patients with meconium ileus although it is well known that acutely ill male neonates have a worse prognosis than comparable female neonates¹⁸. Male children with cystic fibrosis tend to do better than equivalent female patients^{19,20} but this has not been the case for children under 1 year of age in our study.

Acknowledgements

The authors would like to thank all their surgical paediatric consultant colleagues for allowing them to report on their patients. The authors also thank Miss J. Hyslop and Mrs J. Walker of the medical illustration department for their assistance.

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Case report

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Prepubic sinus: an unusual urachal remnant

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Five cases of congenital prepubic sinus have been previously reported¹⁻³. Three further cases which demonstrate the range of features that may be found in this condition are presented.

Case reports

Patient 1

A male infant was found at birth to have a polypoid midline lesion at the upper border of the pubis, with an associated fistula (Figure 1). No abnormality was found on ultrasonography of the renal tracts. Results of cystoscopy were normal, with no evidence of outlet obstruction. Exploration was performed when he was 2 months old. The fistula was found to pass through the symphysis pubis and over the anterior aspect of the bladder to open into its apex. The track was completely excised with a core of pubic cartilage and the bladder defect was closed. Histological examination showed a cord of smooth muscle lined by transitional epithelium.

Patient 2

A 2-year-old girl presented with a chronically discharging congenital prepubic pit. Results of cystoscopy were normal. At operation a sinus track was found to run over the superior aspect of the pubis and was lying on the anterior aspect of the bladder. There was no communication with the bladder cavity and complete excision was performed. The sinus was lined with pseudostratified epithelium.

Patient 3

A female infant was noticed at birth to have a small midline prepubic sinus. Ultrasonographic examination of the renal tracts was normal. The sinus was excised when the child was 2 years old. The 5-cm track passed over the pubis but did not reach the bladder. Histological examination revealed a central lumen, lined with transitional epithelium, surrounded by a muscular connective tissue wall.

All three children had normal external genitalia and clinically normal micturition. None had diastasis of the pubic symphysis.

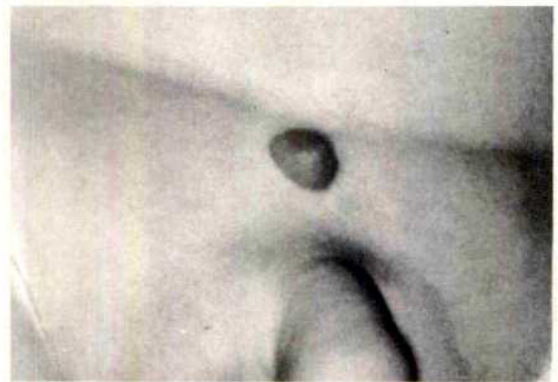


Figure 1 Patient 1: polypoid opening of midline prepubic fistula

Discussion

Congenital prepubic sinus may present to the general, paediatric or urological surgeon. External appearances may be misleadingly insignificant and probing, ultrasonography and sinography will not always demonstrate the extent of the lesion. In other urachal remnants complete excision is necessary to prevent recurrence of symptoms⁴ and late malignant change⁵. As the congenital prepubic sinus or fistula appears to be a urachal variant, the operating surgeon must be prepared for a dissection which may lead to the dome of the bladder. The track and any surrounding cartilage should be removed *en bloc*. A Pfannenstiel incision gives adequate and safe exposure.

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Technique for laparoscopic appendicectomy

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Laparoscopic appendicectomy was introduced by Semm¹ in 1983. Several modifications of his technique have been described^{2–5}, all of which involve resection of the appendix within the peritoneal cavity and subsequent removal. This paper describes a technique for excising the appendix after delivering it laparoscopically through the abdominal wall, minimizing intra-abdominal dissection.

Surgical technique

Between August 1990 and April 1991, laparoscopic appendicectomy was performed in 31 patients (28 as an emergency and three as elective procedures). Patients under the age of 15 years were not included. The technique was employed whenever possible, subject only to the availability of the surgeons and equipment. All patients received antibiotic prophylaxis with metronidazole, 1 g rectally 1 h before surgery or 500 mg intravenously at induction of anaesthesia.

Peritoneal insufflation with carbon dioxide was produced by means of a Verres needle introduced infraumbilically. Insufflation was controlled by automatic regulation to a maximal intraperitoneal pressure of 15 mmHg. Once the pressure was achieved, a 10-mm disposable trocar and cannula (Auto Suture, Ascot, UK) was introduced at the same site and a 10-mm Hopkins end-viewing laparoscope (Olympus Optical, Tokyo, Japan) inserted to inspect the peritoneal cavity and confirm the diagnosis. A second incision was made over McBurney's point and a 12-mm trocar and cannula introduced under direct vision at this site. The tip of the appendix was grasped with forceps and brought up into the lumen of this cannula. Gentle traction on the omentum was sometimes required to tease off inflammatory adhesions before this was achieved. Cannula and appendix were then withdrawn together, delivering the appendix on to the surface. It was manipulated through the wound until the pole of the caecum became visible. This manoeuvre was facilitated by evacuation of gas from the abdominal cavity allowing the anterior abdominal wall to fall back on to the caecum. The mesoappendix was ligated and divided and the appendix stapled using a TA30 stapler (Auto Suture) or ligated and excised. The stump was inspected and cauterized as necessary. The caecum was returned to the abdominal cavity, and the stump and surrounding area irrigated with tetracycline solution. The cannulae were withdrawn after evacuating the carbon dioxide from the abdomen. Tetracycline was instilled into the wounds which were closed with subcuticular absorbable sutures or skin staples. Where the appendix could not easily be delivered owing to peritoneal attachments or inflammatory adhesions, a third trocar and cannula (5 mm) was introduced suprapubically in the midline or slightly to the left to avoid instrument crowding. Dissecting instruments and diathermy were then used to mobilize the appendix and caecum before proceeding.

The appendix may be so oedematous or friable that it cannot be drawn into the lumen of the 12-mm cannula. The cannula can then be removed and the appendix and mesoappendix grasped close to the caecum with a Babcock's forceps introduced directly through the wound. The appendix can then be manipulated gently on to the surface.

After discharge patients were reviewed at 7–10 days and at monthly intervals until full recovery. All wounds were inspected at each visit.

Results

The technique was successful in 25 patients, and in 14 only two cannulae were needed. In 11 patients an extra cannula was

introduced to allow dissection of the appendix from surrounding structures, and two retrocaecal appendices were freed by division of the lateral peritoneal reflection of the caecum.

In six patients the operation was converted to open appendicectomy by extending the incision at McBurney's point. Technical difficulties in two patients were omental insufflation with the Verres needle, resulting in a restricted view, and abdominal wall adiposity. Disease-related difficulties included four patients with dense inflammatory adhesions or small bowel dilatation; these problems occurred in patients whose symptoms had been present for more than 72 h.

The diagnosis of acute appendicitis was confirmed histologically in 23 patients. Acute salpingitis was diagnosed in one patient and the normal appendix removed. In four patients presenting acutely no definitive diagnosis was achieved and the appendix was histologically normal. In the three patients undergoing elective operation, histological evidence of previous appendicitis was found.

The mean operating time was 62 (range 18–135) min. The median time to discharge was 2 (range 1–4) days and the median time to resumption of normal activity 14 (range 7–28) days.

Two patients whose operations were converted to open appendicectomy experienced prolonged postoperative ileus which in one patient necessitated re-exploration and division of adhesions. The decision to abandon laparoscopic appendicectomy was made early owing to inability to locate the appendix behind dilated small bowel loops and densely adherent omentum. The postoperative problems were caused by the severe inflammation and intra-abdominal sepsis associated with the primary pathology and not by the initial laparoscopy.

Four patients recovered uneventfully from open appendicectomy.

Discussion

In the original description of laparoscopic appendicectomy¹, the mesoappendix and appendix were dissected, ligated and divided within the peritoneal cavity. The appendix was then withdrawn through a cannula, avoiding contact with the wound edges. Gotz *et al.*⁵ reported 388 patients undergoing laparoscopic appendicectomy by this method and claimed not to have any severe wound infection. The technique described in this paper involved contact between appendix and wound, but no infections of the latter were seen. One patient reported some erythema around the right iliac fossa wound which resolved spontaneously.

The main advantage of this technique is that the vessels and appendix are divided under direct vision. The appendix stump was stapled in most cases but it can easily be ligated and invaginated. Invagination of the stump is probably unnecessary⁶.

Operating time varied considerably and was influenced by the number of inflammatory adhesions and patient obesity. The most important factor was the experience of the operator. The decrease in mean operating time by one member of the surgical team was from 86 min for the first four patients to 28 min for patients 11 to 14. A similar but less pronounced learning curve was apparent for other, less experienced operators.

The conversion rate to open appendicectomy (19 per cent) was similar to the early results of Gotz *et al.*⁵; they noted a reduction to 3 per cent with greater experience.

Obesity presents a problem in that the distance through which the appendix and caecum are to be manipulated is increased by the thickness of the abdominal wall. By appropriate placement of the cannulae and more extensive intra-abdominal mobilization this can usually be overcome.

These patients may benefit most by avoiding what would otherwise be a relatively long incision.

This therapeutic application adds to the diagnostic value of laparoscopy and may reduce the need for exploratory laparotomy in patients with lower abdominal peritonitis of uncertain aetiology.

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Announcement

The International Association for the Surgery of Trauma and Surgical Intensive Care (IATSIC) was founded in Toronto in 1989 during International Surgical Week. It is an affiliated association of the International Surgical Society.

The Society has become an immediate success and was responsible for five main sessions on trauma and intensive care at the Stockholm meeting last year. A British chapter has been formed with Professor Brian Rowlands (Belfast) as Chairman and Mr Alberic Fiennes (St George's, London) as Secretary. Any surgeon interested in joining this new Association should contact the Secretary at the following address: Mr Alberic G. T. W. Fiennes, Senior Lecturer, Department of Surgery, St George's Hospital Medical School, Jenner Wing, Cranmer Terrace, London SW17 0RE, UK.

Miles Irving

Siting a transverse colostomy

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Traditional teaching suggests that a transverse colostomy should be sited in the right upper quadrant. This study of 67 colostomies (26 right upper quadrant and 41 right iliac fossa) indicates that they should be placed in the optimum position for each patient, which is usually the right iliac fossa.

The site of election for a transverse colostomy is said to be the right upper quadrant, midway on a 45° line joining the umbilicus and costal margin (Figure 1)¹⁻⁹. This recommendation was based on previous methods of managing colonic obstruction and elective resection of left-sided large bowel tumours.

In those with a large bowel obstruction it was usual to perform a 'blind' colostomy through a limited transverse incision, as an initial and often life-saving procedure. In 1894 Sutton¹⁰ underlined the advantages of a concomitant laparotomy.

In the 1930s a defunctioning colostomy in the right upper quadrant was carried out as a preliminary to resection of large bowel tumours (popularized by Devine¹¹). This created the most favourable conditions for anastomosis at a time when bowel preparation was rudimentary and antibiotic prophylaxis non-existent. The colostomy was performed through a limited incision several days before the definitive resection to allow the distal bowel to be prepared. It was retained to defunction the anastomosis.

In both these procedures the colostomy was performed blind through a small incision without laparotomy. The right upper quadrant was used because this was where the colon could most readily be found.

Currently a temporary colostomy is constructed to protect a low anastomosis or to defunction an anastomotic leak. In these circumstances the abdomen is open and the transverse colon can be brought to reach a more favourable site.

Patients and methods

A retrospective review of transverse loop colostomies performed over a 4-year period (1986-1990) was carried out. Data were collected from clinical and stoma care service records.

Technique

The exact position of the stoma was assessed for each patient and marked before operation. It usually lay two-thirds of the way along a line drawn from the anterior superior iliac spine to the umbilicus.

The transverse colon is mobile and it was not usually necessary to mobilize the hepatic flexure unless there were adhesions from previous surgery. In two patients in whom a blind colostomy was performed, there was no difficulty in finding the transverse colon through a small incision in the right iliac fossa. The transverse colon was brought through the body of the rectus muscle or lateral to it. It is important that the stoma should be formed from colon to the right of, and preserving, the middle colic artery to avoid devascularization of a left-sided colonic anastomosis.

Twenty-six colostomies were situated in the right upper quadrant and 41 in the right iliac fossa. Four patients with right iliac fossa colostomies did not have them closed, in three because of disease progression and the fourth patient was too frail. All patients with right upper quadrant colostomies had them reversed.

Results

In the right upper quadrant group, patients complained that they could not see the stoma adequately and three reported that the appliance interfered with bending, sitting and wearing

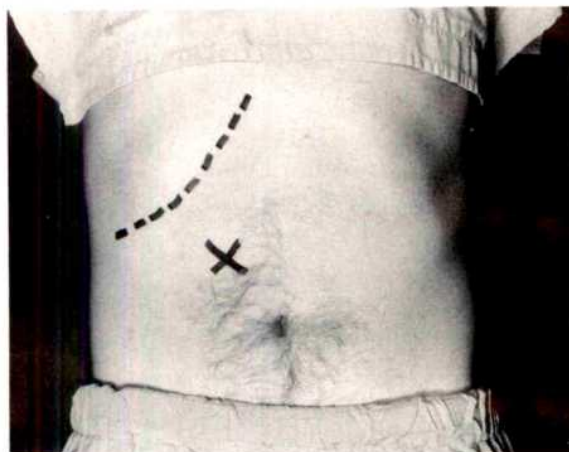


Figure 1 Traditional siting of a transverse colostomy (midway on a 45° line joining the umbilicus to the right costal margin) with the patient lying supine as on the operating table. The cross indicates the site of election of the stoma

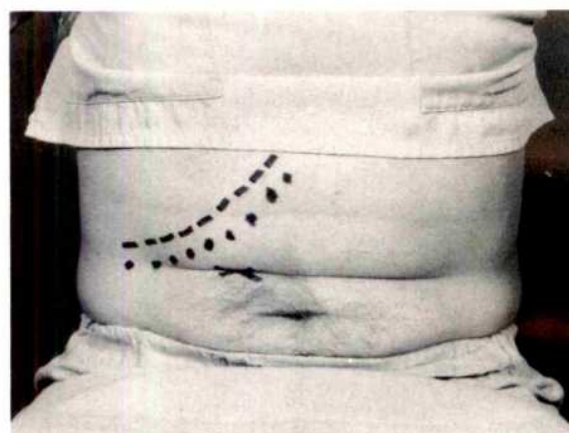


Figure 2 The same site as in Figure 1 with the patient in the sitting position: the stoma site would lie in a skin crease. Note also the projection of the costal margin on the abdominal wall, shifting to a lower and potentially uncomfortable position (dotted line)

clothes, leading to a restricted lifestyle. Another five patients required special attention by the stoma care sister to improve the adherence of the bag to uneven surrounding skin.

No patients in the right iliac fossa group complained of any problems. Most volunteered that the low location of the bag simplified toileting and emptying routines. Mild prolapse of the stoma occurred in two patients in this group but this was easily controlled and did not interfere with the appliance. No parastomal hernias occurred in either group.

Discussion

A colostomy in the right upper quadrant may be associated with several problems; it is a difficult area for the patient to visualize when changing an appliance, especially in large-breasted women, in those with neck stiffness, or when a prominent costal margin creates a 'shelf'. The bag encroaches on the waistline making it impossible for the patient to conceal, and interferes with clothing when the patient sits or leans forward. The right upper quadrant is a frequent site for a skin crease, which may result in leakage. Although the stoma may be free of the costal margin when the patient is lying on the operating table, when sitting the lower ribs may impinge upon it, resulting in an uneven contour for an appliance (*Figure 2*).

Prolapse of the stoma is a potential complication of loop colostomy. The right iliac fossa site should not lead to an increased incidence of this problem. Its minor occurrence in two patients in this group was easily managed.

The right iliac fossa has been advocated as the site of election for a diverting loop ileostomy^{12,13}. The advantages of this location are stressed but it is unclear whether it should be recommended as an alternative to a colostomy. Its closure may be associated with an increased incidence of complications^{14,15}.

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Colonic anastomosis using the biofragmentable anastomotic ring and manual suture: a prospective, randomized study

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One hundred and fifty consecutive patients undergoing colonic surgery were randomized into two groups: 71 underwent hand-suture with a two-layer anastomosis of resorbable suture material (3/0 Dexon) and 79 were fitted with the biofragmentable anastomotic ring (Valtrac – BAR). Five patients, two treated using the BAR and three by suturing, developed anastomotic leakage which required a Hartmann-type reoperation. This was successful in four; one patient in the suture group died after reoperation. One patient who underwent suture had an early anastomotic stricture with fatal sequelae. Three other patients (one in the BAR group and two in the suture group) died after operation from other causes. Thus the mortality rate was 6 per cent in the suture group and 1 per cent in the BAR group. During follow-up, one patient in each group underwent reoperation for anastomotic stricture. Recovery of the gastrointestinal tract was similar in the two groups regarding duration of nasogastric drainage, intravenous fluid therapy and ileus. There was no difference between the groups in duration of hospital stay. The BAR seems to be a safe and reliable alternative to conventional suture anastomosis in colonic surgery.

The biofragmentable anastomotic ring (Valtrac – BAR; Davis and Geck, Wayne, New Jersey, USA) was introduced in 1985 by Hardy *et al.*¹. It is a double-segmented ring composed of polyglycolic acid (Dexon; Davis and Geck) and barium sulphate, originally designed for colonic anastomosis^{1,2}. In about 3 weeks the ring breaks up within the bowel lumen and the fragments are passed in the faeces, leaving no foreign material in the tissues. The aim of this randomized study was to compare the efficacy of the BAR anastomosis with conventional two-layer suture anastomosis in colonic surgery.

Patients and methods

All patients undergoing open colonic surgery between 1 June 1988 and 28 February 1991 were considered for inclusion in the study. Patients were randomized at laparotomy if a procedure requiring a colonic anastomosis was deemed necessary. Only if the bowel lumen was too narrow for insertion of the smallest BAR (outer diameter 28 mm) was the patient excluded from the study.

Seventy-nine patients were allotted to the BAR group and 71 to receive manual sutures (*Table 1*). The mean age was 61 years. Purse-string sutures for anchoring the bowel ends to the centre tube of the BAR were polyglycolic acid monofilament (3/0 Maxon; Davis and Geck); a purse-string clamp was used. For manual suture of the anastomosis polyglycolic acid multifilament (3/0 Dexon; Davis and Geck) was used in two layers with an inversion technique; the inner suture was continuous and the outer was interrupted. All anastomoses were constructed end-to-end.

The postoperative course was followed by recording the number of days of nasogastric drainage; drainage was discontinued when the volume was < 500 ml/day. The number of days of intravenous fluid therapy, the time taken to return to an oral diet, and the time to appearance of bowel movements were also recorded.

All complications were noted. After discharge from hospital patients were followed up as outpatients; mean follow-up was 11 (range 1–33) months. Operations were performed by five surgeons, three of whom were qualified abdominal surgeons and two senior registrars.

Statistical analysis was carried out using the χ^2 test, with $P \leq 0.05$ taken as significant.

Table 1 Study population allotted to colonic anastomosis by biofragmentable anastomotic ring or conventional suture

	Total	Method of anastomosis	
		BAR	Suture
M	78 (52)	46 (58)	32 (45)
F	72 (48)	33 (42)	39 (55)
Total	150 (100)	79 (100)	71 (100)
Reason for operation			
Malignancy	72 (48)	35 (44)	37 (52)
Other	78 (52)	44 (56)	34 (48)

Values in parentheses are percentages. BAR, biofragmentable anastomotic ring

Results

In all, 133 colocolic and 17 ileocolic or ileorectal anastomoses were performed (*Table 2*). A colorectal anastomosis below the peritoneal reflection was performed in 16 patients, of whom eight fell into each treatment group. The operation was performed electively in 136 patients and as an emergency in 14.

Surgical complications are listed in *Table 3*. The five patients with anastomotic leakage were treated with a Hartmann's procedure. Four patients survived this reoperation; one patient receiving sutures, who had been operated on for carcinoma of the splenic flexure, died. One of the sutured patients was readmitted and operated on for obstruction 2 weeks after a right hemicolectomy for carcinoma. An anastomotic stricture, probably of ischaemic origin, was found and the patient subsequently died. Three further patients died after operation, one with the BAR and two in the suture group, although in none of these was the cause of death related to the anastomosis. The mortality rate for patients treated with the BAR was 1 per cent (one of 79), and 6 per cent (four of 71) for those in the suture group. Two patients treated with the BAR and one

Table 2 Operations performed on 150 patients

	Total	Method of anastomosis	
		BAR (n = 79)	Suture (n = 71)
Anterior resection	53	25 (32)	28 (39)
Hemicolectomy			
Right	29	13 (16)	16 (23)
Left	17	9 (11)	8 (11)
Closure of colostomy	17	12 (15)	5 (7)
Ileocaecal resection	10	6 (8)	4 (6)
Subtotal colectomy with ileoproctostomy	7	4 (5)	3 (4)
Resection of splenic flexure	5	4 (5)	1 (1)
Resection of transverse colon	2	1 (1)	1 (1)
Other	10	5 (6)	5 (7)

Values in parentheses are percentages. BAR, biofragmentable anastomotic ring

Table 3 Complications after operation

Complication	Total	Method of anastomosis	
		BAR (n = 79)	Suture (n = 71)
Anastomotic leakage	5	2	3
Wound infection and/or dehiscence	6	3	3
Anastomotic stricture	4	2	2
Acute	1	0	1
Late	3	2	1
Intraluminal anastomotic bleeding	3	2	1
Total	18	9	9

BAR, biofragmentable anastomotic ring

with a sutured anastomosis had intraluminal bleeding leading to rectal haemorrhage during the first few days after operation. These patients were treated conservatively and made uneventful recoveries.

During follow-up three patients developed anastomotic stricture. Two had been treated using the BAR; one of these patients, who had undergone sigmoid resection, had frequent, painful defaecation, and the stools were tape-like. At sigmoidoscopy 10 weeks after operation the anastomosis appeared oedematous and narrowed. The symptoms gradually subsided and no intervention was needed. The other patient with a BAR anastomosis developed partial intestinal obstruction about 3 months after left hemicolectomy for diverticulosis. A barium enema demonstrated the strictured anastomosis and some residual diverticula. Re-resection of the anastomotic area resulted in an uneventful recovery. One patient with a sutured anastomosis developed an anastomotic stricture with obstruction and was reoperated on 3 months after a colonic resection for villous adenoma.

Table 4 shows the recovery of the gastrointestinal tract. Need for nasogastric intubation, duration of intravenous fluid therapy, first productive bowel movements and tolerance of oral feeding were similar in both groups. The duration of the hospital stay after operation was also similar (Table 5).

Discussion

The BAR differs from its predecessor, Murphy's button³, and some of the later compression anastomotic devices^{4,5} in that it does not cause necrosis in the inverted bowel ends after ring

Table 4 Recovery of the gastrointestinal tract after operation

Recovery-related variable	Total	Method of anastomosis	
		BAR (n = 79)	Suture (n = 71)
Duration of nasogastric drainage (days)			
> 2	33	18 (23)	15 (21)
2	52	28 (35)	24 (34)
1	65	33 (42)	32* (44)
Duration of total intravenous fluid therapy (days)			
> 3	25	13 (16)	12 (17)
3	23	16 (20)	7 (10)
≤ 2	102	50 (63)	52 (73)
Time until regular diet tolerated (days)			
≥ 7	37	20 (25)	17 (24)
6	54	31 (39)	23 (32)
≤ 5	59	28 (35)	31 (44)
Time until first defaecation (days)			
≥ 6	41	20 (25)	21 (30)
5	53	30 (38)	23 (32)
≤ 4	56	29 (37)	27 (38)

Values in parentheses are percentages. *Tube in one patient removed immediately after operation. BAR, biofragmentable anastomotic ring

Table 5 Duration of hospital stay after operation

Hospital stay (days)	Total	Method of anastomosis	
		BAR (n = 79)	Suture (n = 71)
> 8	54	26 (33)	28 (39)
8	32	17 (22)	15 (21)
7	51	26 (33)	25 (35)
≤ 6	13	10 (13)	3 (4)

Values in parentheses are percentages. BAR, biofragmentable anastomotic ring

closure. Its biofragmentability is a unique feature. The BAR has some obvious advantages over other methods of construction of colonic anastomoses. It is easy to use and the procedure may be performed swiftly; it produces a standardized and safe anastomosis^{2,6}. Experimental work has shown the BAR anastomosis to be similar in macroscopic and histological appearance to that of hand-sewn and stapled anastomoses at 40 days after operation⁷.

The overall incidence of anastomotic leakage in the present series was 3.3 per cent, comparable to that of other studies of colonic anastomosis^{8,9}. The occurrence of anastomotic stricture was acceptably low at 2.7 per cent. The present observations are in accordance with those of a recent multicentre study by Bubrick *et al.*¹⁰, but differ from the results of Luukkainen *et al.*¹¹, who observed more anastomosis-related complications in the BAR group. All present leakages were significant and required reoperation.

In the early period after surgery a mechanical anastomotic device may cause obstruction in the bowel lumen, as has been demonstrated experimentally⁷. However, in the present series there was no significant difference between the groups in the recovery of the gastrointestinal tract. The risk of obstruction with the BAR seems no greater than that experienced after conventional anastomotic techniques.

These observations suggest that the BAR is a safe and reliable alternative to conventional sutured anastomosis. The device is currently in routine use for colonic surgery in this clinic.

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Reduction of mucosal crypt cell proliferation in patients with colorectal adenomatous polyps by dietary calcium supplementation

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The crypt cell production rate was measured in 14 patients with adenomatous colorectal polyps, 17 patients with colorectal cancer and 12 control subjects. The median (interquartile range) rate (cells per crypt per hour) was found to be significantly higher ($P < 0.001$) in the polyp (2.45 (1.94-3.20)) and cancer (3.01 (2.35-3.68)) groups compared with controls (1.25 (0.70-1.85)). A double-blind cross-over study was performed in patients with adenomatous polyps consisting of 2 months' treatment, 2 weeks' washout, followed by 2 months' treatment with dietary calcium supplementation (1.25 g day⁻¹) versus placebo. A significant reduction in the crypt cell production rate occurred with calcium treatment compared with the placebo (1.25 (0.6-2.25) versus 2.15 (1.58-3.08) cells per crypt per hour, $P = 0.035$). This study demonstrates a significant reduction in mucosal cell proliferation by dietary calcium supplementation in patients with adenomatous polyps. Such treatment may be worthy of further investigation in patients at high risk of developing colorectal polyps.

There is strong evidence that increases in mucosal cell proliferation precede the development of colonic cancer in humans and in animal models^{1,2}. Expansion of the colonic crypt cell proliferative compartment has been demonstrated in patients with familial adenomatous polyposis³⁻⁵, in subjects with a history of familial or non-familial colonic cancer⁶⁻⁸, and in patients with sporadic adenomas⁹⁻¹¹ or ulcerative colitis¹²⁻¹⁵.

Wargovich *et al.*¹⁶ showed that dietary calcium significantly lowered the toxicity of bile acids, which are implicated in the pathogenesis of colorectal polyps and cancer. Free bile acids (representing 98 per cent of colonic bile acids) and fatty acids are precipitated in the colon as calcium phosphate complexes or soaps, provided there is sufficient calcium in the diet¹⁷⁻¹⁹. A number of experimental studies has suggested that this is the mechanism of action of dietary calcium in reducing colorectal carcinogenesis^{16,18,20-23}. Alternatively, calcium may have a direct inhibitory effect on colonic cellular proliferation²⁴.

Epidemiological studies have suggested that calcium reduces the risk of colorectal cancer^{25,26} but the data are conflicting²⁷. Of four dietary intervention studies undertaken²⁸⁻³¹, only one did not reveal a reduction in colonic crypt cell proliferation by dietary calcium³⁰. There has been no detailed study, however, of calcium supplementation in patients with adenomatous polyps.

The effects of supplementary dietary calcium on mucosal cell proliferation using a double-blind cross-over study were, therefore, investigated in a group of patients with adenomatous polyps. The colonic crypt cell production rate (CCPR) was examined in patients with colorectal cancer because the technique used is stathmokinetic^{32,33} and differs from that in other studies mentioned above, which used the tritiated thymidine labelling index.

Patients and methods

Study design

The rectal CCPR was measured in a group of control patients, a group with adenomatous polyps and a group with colorectal cancer. Rectal biopsies (2 mm thick) were obtained by rigid sigmoidoscopy from the posterior wall, 10 cm from the anal verge or at least 5 cm from a rectal

tumour if present. Patients with histological evidence of proctitis were excluded, as was any patient with a recent change from normal bowel habit (other than bleeding). None of the control subjects or patients had a family history of colorectal cancer. All the individuals were white Caucasians, taking a free-range omnivorous diet.

The effect of calcium supplementation on rectal CCPR was assessed in the adenomatous polyp group using a double-blind cross-over study. The treatment was dispensed by the pharmacy in coded form with precise instructions to each patient, and prescriptions randomized by the pharmacy before the start of the trial using random number generation. The calcium and placebo were in powder form. The dose of calcium was 1.25 g day⁻¹ given as calcium gluconate (BDH, Atherstone, UK). The placebo was lactose powder, a substance known not to affect bowel habit in the absence of lactose intolerance, which was excluded by history. The study period consisted of 2 months on the first treatment followed by a 2-week washout period before starting on the second powder for a further 2 months.

Patients

The control group consisted of six men and six women with a median (interquartile range (i.q.r.)) age of 64 (52-71) years. The patients were included as controls only if the large bowel was shown to be free of neoplastic lesions by rigid sigmoidoscopy and a double contrast enema. The diagnoses were haemorrhoids ($n = 8$), diverticular disease ($n = 2$) and non-specific abdominal pain ($n = 2$). Patients with irritable bowel syndrome were excluded. The adenomatous polyp group consisted of eight men and six women with a median (i.q.r.) age of 64 (52-73) years. All had villous adenomas, which were solitary in all but two. There were 17 patients with colorectal cancer, of whom ten were men. The median (i.q.r.) age was 72 (57-78) years. Eleven cancers were rectal, four were rectosigmoid, and two were in the sigmoid colon. Three cancers were classified as Dukes' A, nine as Dukes' B and five as Dukes' C.

Crypt cell production rate

Measurement of CCPR was based on previously described techniques^{32,33}. Biopsies were immediately placed into a circular Perspex dish (Falcon Plastics, Los Angeles, California, USA) containing RPMI 1640 (Gibco, Paisley, UK) organ culture medium with added gentamicin (40 mg ml⁻¹), penicillin (100 units ml⁻¹) and fetal calf serum (1:9, vol:vol). The medium was equilibrated with 95 per cent oxygen and 5 per cent carbon dioxide at 37°C for 1 h before use. The dish was incubated at 37°C in the above gas mixture. After 16 h the medium was replaced with identical medium but containing 0.4 g ml⁻¹ vincristine (Eli Lilly, Basingstoke, UK). Biopsies were

removed 60, 120 and 180 min later, fixed in Carnoy's solution for 2–6 h and stored in 70 per cent ethanol.

After rehydration the specimen was hydrolysed in 1 mmol l⁻¹ hydrochloric acid for 6 min at 60°C, stained with Schiff's reagent and rinsed with 45 per cent acetic acid. The mucosa was microdissected from each specimen and the number of arrested metaphase figures in ten crypts per specimen was counted by one person (D.Y.) on coded samples. Linear regression analysis was used to determine the slope of metaphase accumulation and was expressed as cells per crypt per hour.

Ethical approval

Approval to undertake the study was obtained from the ethical committees of the Central and West Birmingham Health Authorities.

Statistical analysis

Comparisons between multiple groups or multiple time-points were undertaken using the Kruskal–Wallis test adjusted for ties. If this was significant, paired analysis was performed using the two-tailed Mann–Whitney *U* test. Significance was taken as *P* < 0.05.

Results

There was no significant difference in the ages between any of the groups. The median (i.q.r.) CCPRs in the three groups were: control group 1.25 (0.70–1.85) cells per crypt per hour; polyp group 2.45 (1.94–3.20); and cancer group 3.01 (2.35–3.68). This was significant overall (*H* = 21.8, 2 d.f., *P* < 0.001). Compared with controls, values were significantly higher for the polyp (*P* < 0.001) and cancer (*P* < 0.001) groups but there was no difference between the latter two. Individual data are shown in Figure 1.

In the cross-over part of the study, calcium supplementation significantly reduced the CCPR in the patients with polyps (*F* = 0.034). For simplicity, data for patients on calcium supplementation or placebo were grouped (Table 1); individual data are shown in Figure 2.

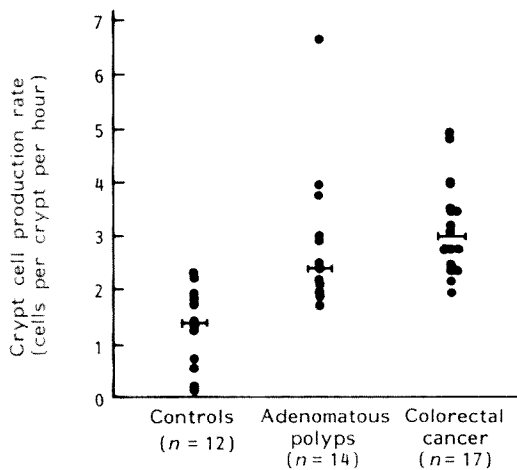


Figure 1 Crypt cell production rates of individuals in the three groups. Bars are median values

Table 1 Summary data of cross-over study in the 14 patients with adenomatous polyps

Median crypt cell production rate (cells per crypt per hour)			Kruskal–Wallis test (2 d.f.)	
Before treatment	Calcium	Placebo	<i>H</i>	<i>P</i>
2.25 1.78–3.1)*	1.25 (0.6–2.25)†	2.15 (1.58–3.08)‡	6.81	0.034

Values in parentheses are interquartile ranges. **P* = 0.022 (before treatment versus calcium); †*P* = 0.035 (calcium versus placebo); ‡*P* not significant (before treatment versus placebo); all two-tailed Mann–Whitney *U* test

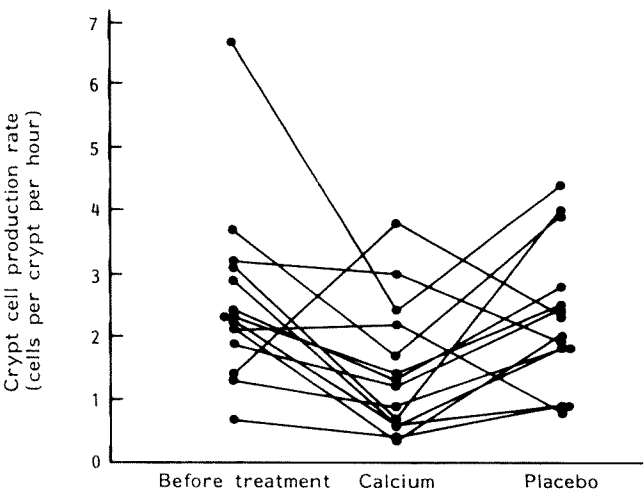


Figure 2 Crypt cell production rates of patients with adenomatous polyps, before and after treatment with calcium or placebo

Discussion

The stathmokinetic method used in this study differs from the tritiated labelling index method but provides an excellent measure of mucosal cell proliferation because it takes into account the cell cycle time, growth fraction and the crypt cell population²⁴. Despite differences in technique these findings are consistent with those from other studies which have shown an increase in mucosal cell proliferation in patients with colorectal polyps or cancer^{1,4,35,36}. The tendency to develop synchronous or metachronous tumours may be related to the finding of a hyperproliferative state throughout the colonic mucosa¹¹. Reduced proliferative activity, however, has been found in Seventh-Day Adventist vegetarians, a group with a lower mortality rate from colonic cancer than the general population in the USA³⁷.

In agreement with previously published studies^{28–31,38}, this study suggests that supplementary calcium intake in double the normal daily amount reduces the CCPR in patients at risk of developing colorectal cancer. Lipkin and Newmark²⁸ showed a reduction in the labelling index of ten individuals at high risk from non-polypoid cancer of the colon. Buset *et al.*²⁹ showed a reduction in cellular proliferation in six of nine individuals with a previously determined high labelling index (four with a family history, four with tumours and one with neither). Using a similar technique Rozen *et al.*³¹ showed a reduction of cell proliferation in a group of 26 first-degree relatives with sporadic colorectal cancer and nine patients who had previously undergone adenoma resection. In the only previous double-blind study (non-cross-over), Gregoire *et al.*³⁰ studied 15 patients after resection for cancer and 15 control subjects. The labelling index appeared to increase after calcium supplementation (*P* = 0.06), perhaps due to instability of colonic crypts following resection.

Calcium supplementation of several grams per day results in minimal variation of serum calcium and has been shown to be safe in several long-term human studies^{39–42}. An intake of 1500 mg day⁻¹ has been recommended to prevent osteoporosis in postmenopausal women without causing ill effects⁴³. The 8-week duration of treatment with calcium or placebo was chosen to ensure that exposure was long enough to exert an effect on intestinal cell kinetics. The normal turnover time of ileal epithelial cells is only a few days. Within 1 week of altering dietary intake the intestinal epithelium can change its proliferation pattern⁴⁴.

In conclusion, calcium supplementation caused a reduction in the mucosal cell turnover rate of patients with colorectal polyps. Whether such an approach can prevent or delay the development of colorectal polyps can be determined only by long-term studies.

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Evaluation of tissue oximetry in perioperative monitoring of colorectal surgery

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Twenty patients undergoing elective colorectal surgery were studied during and after operation by means of tissue oximetry measuring the subcutaneous partial pressure of oxygen (P_{scO_2}) and by gastric intramural pH measurement. Mean(s.d.) P_{scO_2} recorded 24 h after surgery was significantly lower than the preoperative value: 14(10) versus 24(14) mmHg, $P < 0.02$. The postoperative P_{scO_2} was also significantly lower than that measured in a control group of ten healthy volunteers: 14(10) versus 34(18) mmHg, $P < 0.001$. The preoperative P_{scO_2} of the patients who developed a postoperative complication was significantly lower than that of those who had an uneventful postoperative clinical outcome: 16(9) versus 32(14) mmHg, $P < 0.02$. The preoperative P_{scO_2} of the patient group with complications was also significantly lower than that of the control group: 16(9) versus 34(18) mmHg, $P < 0.02$. The preoperative P_{scO_2} of the group of patients without complications was almost identical to that of the control group. During operation only one patient developed gastric intramural acidosis. Perioperative oxygen debt and the response of subcutaneous tissue oxygen tension to oxygen breathing seemed to correlate better with clinical outcome than gastric wall pH values and the conventional parameters of tissue perfusion.

The adequacy of oxygenation and perfusion of peripheral tissues is not precisely assessed by classical monitoring techniques in the intensive care unit. These techniques reflect only the patient's central haemodynamic condition^{1,2}.

Useful information about the perfusion and oxygenation of the splanchnic bed is available using a non-invasive technique³ which measures gastric intramural pH (pH_i). A previous study has demonstrated the prognostic value of pH_i in short-term clinical outcome of surgical patients in intensive care⁴.

Subcutaneous tissue partial pressure of oxygen (P_{scO_2}) measurements provide direct information about tissue perfusion and oxygenation, and correlate more accurately with haemodynamic status than traditional perfusion parameters.

In the present study, the above variables (pH_i and P_{scO_2}) have been compared with conventional parameters of perfusion (urinary output, arterial blood pressure, pulse rate and haematocrit) in patients undergoing colorectal surgery. The results were related to clinical outcome in a more detailed way than in a previous report from this department⁵.

Patients and methods

Subcutaneous oximetry was performed as described by Gottrup and colleagues² using a calibrated ammeter. A gas-sterilized plain Silastic (Dow Corning, Reading, UK) catheter (1 mm outer diameter, 0.8 mm inner diameter, 15 cm long) was introduced subcutaneously in the deltoid region of each patient through a 20-G spinal needle immediately after induction of anaesthesia. Both ends were cut off 1.5 cm from the skin surface. A sheathed platinum needle electrode (needle outer diameter 0.7 mm, electrode tip 25 μ m, model no. 760; Diamond Electrotech, Ann Arbor, Michigan, USA) was inserted so that its tip was at least 1 cm under the skin entrance point. At the opposite end of the Silastic tube a reference electrode was inserted. Both electrodes were connected to the ammeter. A period of 20 min was allowed for the equilibration of gases and temperature. Calibration had been undertaken in a temperature-controlled bath at the patient's body temperature before each set of measurements; a borax solution was used to obtain the zero calibration point. The maximum calibration point was set on ambient barometric pressure values via a conversion

table. In patients who underwent surgery of the rectum or sigmoid colon, oral temperature was monitored continuously. In all the other patients rectal temperature was measured continuously.

During operation, measurements of P_{scO_2} were carried out at 15-min intervals. Postoperative P_{scO_2} measurements were started 24 h after surgery and were made at 5-min intervals for long enough to establish a baseline value consisting of two consecutive readings 5 min apart that differed by no more than 2 mmHg.

The response of P_{scO_2} to breathing oxygen was also evaluated⁶: patients breathing air were given oxygen at 5 l min⁻¹ via a face mask for at least 20 min (fraction of inspired oxygen 60–70 per cent); patients who were already breathing oxygen received it at double the previous rate. If P_{scO_2} rose by 20 per cent or more the patient was categorized as well perfused. This was defined as a positive oxygen challenge test⁶.

pH_i was measured according to the method of Fiddian-Green and Baker³. The value of pH_i was calculated from the Henderson-Hasselbalch equation from the partial pressure of carbon dioxide (P_{CO_2}) of gastric juice and arterial bicarbonate tension. The P_{CO_2} of the gastric juice was measured with a Silastic tonometer which was placed inside the stomach.

The arterial partial pressure of bicarbonate (P_{aHCO_3}) was recorded from an arterial blood sample. A pH of 7.32 was taken as the critical limit for adequate oxygenation of the stomach wall⁴. No attempt was made to influence the amount of fluid given by the anaesthetist. Arterial partial pressure of oxygen (P_{aO_2}) and P_{aHCO_3} were measured every 30 min during the operation. Following current surgical practice, the patient was assessed clinically after operation for the following signs or symptoms of hypoxaemia: dyspnoea, chest pain, crepitations, wheezing, focal signs of infection or collapse, tachypnoea, hypopnoea and cyanosis. When there was any suspicion of hypoxaemia, an arterial blood sample was taken (patients 1, 2, 5, 10, 11 and 16). Arterial hypoxaemia was defined as $P_{aO_2} < 80$ mmHg or an oxygen saturation < 90 per cent. Hypoxaemia was not encountered biochemically and P_{aO_2} always rose by more than 20 per cent after oxygen administration. The P_{aO_2} values in these patients (before/after oxygen administration) were 80/98, 139/187, 172/215, 106/176, 80/125 and 90/127 mmHg. Arterial oxygen saturation was always > 90 per cent. Adequate urine output was defined as ≥ 50 ml h⁻¹. Postoperative complications were noted.

The patient group comprised 20 subjects, 14 men and six women, of mean age 67 (range 23–83) years, undergoing elective colorectal surgery. None of the patients showed clinical signs of pulmonary

dysfunction as assessed by the surgeon and anaesthetist before operation. The operative procedures included four left hemicolectomies, three for carcinoma of the colon (patients 1, 5 and 16) and one reoperation in a patient suffering from Hirschsprung's disease (patient 3). Four anterior resections for rectal carcinoma (patients 10, 14 and 15) or sigmoid carcinoma (patient 18) were performed. Two patients with sigmoid carcinoma (patients 6 and 8) and one with sigmoid diverticulitis (patient 9) were treated by sigmoid colectomy. Two patients with carcinoma of the caecum (patients 2 and 20) and one with carcinoma of the ascending colon (patient 11) underwent resection by right hemicolectomy. Miles' excision of the rectum was performed for carcinoma in three patients (patients 12, 13 and 19). There were two Hartmann resections for a sigmoid carcinoma (patient 7) and a carcinoma of the rectum (patient 17), and one segmental colectomy for carcinoma (patient 4).

Ten patients had an uneventful postoperative course. Complications included four abdominal wound infections (patients 3, 7, 12 and 20), a perineal wound infection (patient 13), an intra-abdominal abscess (patient 9) and anastomotic leakage (patient 2), as well as cholecystitis (patient 1), acute pulmonary oedema and septic shock (patient 11), toxic hepatitis and deep vein thrombosis (patient 4), and wound dehiscence and stress ulceration (patient 12).

In a control group of ten healthy volunteers comprising seven men

and three women of mean age 28 (range 23–60) years, the Silastic catheters were implanted under local anaesthesia. To avoid interference with local anaesthetic, measurements of P_{scO_2} were performed at least 10 h later⁷. Baseline recordings were made and an oxygen challenge test (5 l min⁻¹ oxygen via a face mask) was carried out. Reproducibility of the P_{scO_2} values was confirmed in a healthy volunteer who had two Silastic tonometers implanted in 1 week to measure both baseline values and response to oxygen breathing.

Student's *t* test was used for statistical comparisons.

Results

Patient group

The results of 301 peroperative measurements and 167 postoperative recordings of P_{scO_2} , as well as pH_i , urinary output, blood pressure, haematocrit, P_{aO_2} and the response to oxygen challenge in the patient group, are summarized in Figure 1. During the first hour of the operative procedure, varying values of P_{scO_2} were observed, but these stabilized in all patients after approximately 75 min when a baseline value was established. The mean (s.d.) peroperative baseline value was 24(14) (range

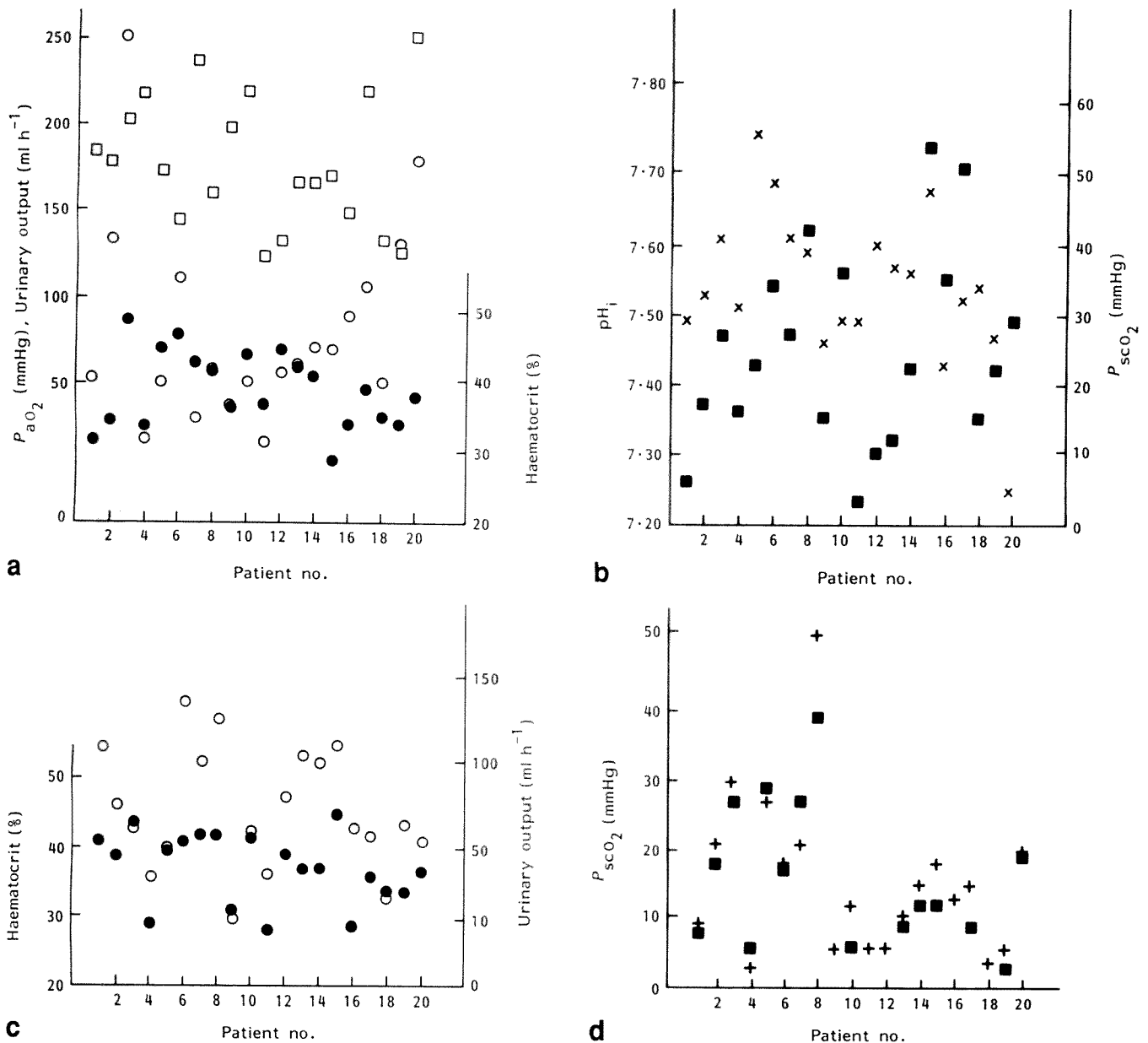


Figure 1 a,b Peroperative and c,d postoperative (day 1) measurements in 20 patients undergoing elective colorectal surgery. Partial pressures of oxygen are arterial (□, P_{aO_2}), subcutaneous (■, P_{scO_2}), and subcutaneous after administration of 5 litres 100 per cent oxygen for at least 20 min (+). (In patients 9, 11, 12, 16 and 18 there was no change in P_{scO_2} after oxygen administration). Other variables measured are urinary output (○), haematocrit (●) and gastric intramural pH (x, pH_i).

3–51) mmHg. Three patients presented with a perioperative baseline value >40 mmHg.

The patients had a baseline P_{scO_2} of 14(10) (range 3–39) mmHg 24 h after surgical intervention.

A significant elevation in P_{aO_2} was noted after operation in all patients, but only six showed a rise in P_{scO_2} of more than 20 per cent above the baseline value in response to breathing oxygen. Thus, 14 patients had a negative oxygen challenge test despite the fact that arterial hypoxaemia was not encountered. Four patients had inadequate perioperative urinary output.

Ten patients developed postoperative complications; in four of these inadequate urinary output was observed, while all ten had a negative oxygen challenge test.

Only one patient (no. 20) had a perioperative pH_i below the critical level of 7.32.

Ten patients made an uneventful postoperative recovery but only four of these showed a negative oxygen challenge test.

The temperatures of all subjects lay within the range 36.2–37.4 °C.

No short-term (within 72 h) death was noted, as predicted by all but one normal pH_i value (111 measurements).

The postoperative P_{scO_2} was significantly lower than that in the control group: 14(10) versus 34(18) mmHg, $P < 0.001$. There was also a significant difference between the perioperative and postoperative P_{scO_2} : 24(14) versus 14(10) mmHg, $P < 0.02$. Figure 1 summarizes perioperative and postoperative results.

Control group

Baseline values of P_{scO_2} (110 measurements: 27, 71, 25, 6, 21, 30, 30, 27, 51 and 51 mmHg) varied widely among the ten healthy volunteers (mean(s.d.) 34(18) (range 6–51) mmHg).

In contrast to patients undergoing operation, all volunteers showed a significant response (>20 per cent rise) to breathing oxygen (P_{scO_2} values 33, 90, 33, 18, 27, 39, 36, 36, 72 and 78 mmHg). All volunteers were normotensive during measurements.

Discussion

Subcutaneous oximetry and gastric intramucosal pH studies can be used to monitor the adequacy of perfusion and oxygenation in the peripheral tissues. Perfusion of the gastrointestinal tract can be assessed³ by calculating the gastric pH_i . Substantial evidence has shown that this can predict short-term mortality in patients in intensive care⁴. Studies in dogs showed that relative changes in subcutaneous blood flow could be demonstrated by using the P_{scO_2} and the Fick principle, suggesting that this was a clinically useful quantifying method for peripheral perfusion^{1,8}. Some studies have suggested that skin and subcutaneous tissue are the first sites to suffer vasoconstriction when submitted to a hypoperfusion state^{7,9,10} and among the last to be restored when this is corrected^{11–13}.

The postoperative P_{scO_2} in this study was significantly lower than that in the control group. There was also a significant difference between the perioperative and postoperative P_{scO_2} values. Patients with an uneventful postoperative clinical outcome were found to have a significantly higher perioperative P_{scO_2} than those with postoperative complications.

There was also a statistically significant difference between the perioperative group with complications and the control group. In contrast, the perioperative P_{scO_2} of the group of patients without complications was almost identical to that of the control group. Thus it becomes evident that surgery has a major effect on peripheral perfusion. Every patient had a postoperative reduction of perfusion independent of a complicated postoperative course. The reduction of perfusion is probably caused by the adrenergic response to injury. It seems, however, that a perioperative predisposition to a complicated postoperative course existed as there was already a statistically significant difference in P_{scO_2} between the patient groups with and without complications. Because no attempt was made to influence fluid management, which was based on

traditional perfusion parameters as ordered by the anaesthetist, a state of hypoperfusion of the subcutaneous and perhaps other 'non-essential' tissues might have developed. The course of surgical intervention itself was not different in the two groups. This hypoperfusion was not shown by the classical parameters, with the exception of an inadequate urinary output in four patients.

A considerable variation in P_{scO_2} values and much lower values than are generally accepted were measured in our study. Several factors might have contributed to this. Fear and pain are factors which cannot be controlled in a reproducible manner. Nevertheless, they probably account for the individual variation in P_{scO_2} values. Subcutaneous temperature was not measured in this study; differences in this may possibly explain the variation in P_{scO_2} . Some studies have suggested that the Silastic tonometer should be implanted at least 2.5 h before any measurement takes place; otherwise, microcirculatory changes owing to its implantation could interfere with the measurements¹⁴. During the perioperative measurements in the present study, a stable value was obtained after approximately 75 min. The technique of tonometer placement used in this study also minimizes the risk of air contamination compared with capillary sampling methods^{7,15}.

A plain Silastic tonometer was used instead of a silver or barium Silastic tonometer, these being more permeable to oxygen¹⁵. Most investigators calibrate their tonometer at a maximum of 150 mmHg. In the present study, the maximum calibration point was defined by using a conversion table in which maximum values depend on ambient atmospheric pressure. Once oxygen leaves the red cell, its diffusion into tissue is controlled solely by its partial pressure, which is dependent on ambient barometrical values¹.

Another possible reason for finding different values in a comparable patient group is a different protocol for measuring baseline P_{scO_2} . Baseline values were measured in patients breathing ambient air in the present study, whereas Chang and colleagues⁷ measured baseline P_{scO_2} in patients who breathed room air for 15 min after previously receiving 5 litres 70–80 per cent oxygen ($n = 10$) or 40 per cent oxygen ($n = 4$) over 1 h. Analysis of other published data shows that stabilized P_{scO_2} values are not reached within 15 min^{2,15,16}.

Other studies have also reported large variations in P_{scO_2} values^{2,6,7,15,17,18}. Most studies accept 60–70 mmHg as a normal P_{scO_2} and 40 mmHg as a critical value in a person breathing air. However, this could not be confirmed in our control group of ten healthy volunteers. In studies by Heppenstall and colleagues¹⁷ and Chang *et al.*⁷, different relationships between the tissue and arterial oxygen tensions were described depending on the type of surgery performed (abdominal or cardiovascular), but no relationship between P_{aO_2} and P_{scO_2} was established in healthy volunteers.

The oxygen challenge test in the present study provided interesting information. Only six patients had a positive response which should indicate that they had an adequate tissue perfusion. They all had an uneventful postoperative course. Of the 14 with a negative response, who were accordingly assumed to be hypoperfused, ten had postoperative complications. Thus there were four false-negative results (positive predictive value 100 per cent, negative predictive value 71 per cent).

Some investigators have suggested that perfusion of the subcutaneous tissue and the gastrointestinal tract changes in a similar way in a hypoperfusion state^{1,19}. Nevertheless, in this study only one patient presented concomitantly with gastrointestinal intramural acidosis and a negative oxygen challenge test. He subsequently developed a postoperative infection despite normal traditional perfusion parameters. In all other patients the gastric pH_i remained normal.

The present study demonstrates a discrepancy between the traditional and new perfusion parameters. Results of perioperative subcutaneous tissue oximetry seem to correlate well with clinical outcome. However, the elaborate calibrations and the method itself are time consuming. Peripheral tissue oximetry might become part of daily clinical monitoring

procedures, but only if it is made simpler and quicker to perform.

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Improving survival rates for patients with colorectal cancer

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Between 1 January 1984 and 31 December 1990, 575 patients were operated on for colorectal cancer. The surgical procedure was performed consistently and no patients were lost to follow-up. Almost half of the patients (284 of 575) had tumours of stage I or II, with 5-year survival rates over 90 per cent. After extending the resection margins in 28 cases of colonic carcinoma there has been no case of tumour recurrence. The overall 5-year survival rate for patients with colonic carcinoma was 81 per cent. Complete resection of the mesorectum was mandatory for rectal resection. One-third of the carcinomas in the lower third of the rectum could be resected with maintenance of bowel continuity and an abdominoperineal resection avoided. Not only was the tumour recurrence rate in the former patients lower (10.5 per cent) compared with that in those undergoing abdominoperineal resection (14.3 per cent) but the 5-year survival rate at 90 versus 52 per cent was significantly higher. The overall 5-year survival rate for patients with rectal carcinoma was 71 per cent.

The concept of extended resection margins in colorectal carcinoma surgery is the result of recent studies suggesting possible lymphogenous spread of carcinoma to a neighbouring lymph drainage zone (Figure 1)¹⁻⁴. As a consequence, the resection of neighbouring lymph drainage zones with ligation of the supplying blood vessels at their origin appears appropriate when a tumour is located close to a border zone.

Dukes⁵ and Westhues⁶ demonstrated that rectal carcinoma metastasizes mainly along the inferior mesenteric artery. Therefore, it is possible radically to resect even a carcinoma of the lower third of the rectum and so preserve continence. A high ligation of the inferior mesenteric artery is obligatory when removing involved N₃ lymph nodes (tumour node metastasis (TNM) system) and is needed to ensure tension-free anastomosis. This procedure may improve the overall survival rate⁷. Goligher⁸ and Heald and Ryall⁹ have successfully demonstrated this approach, with emphasis on complete resection of the mesorectum and minimal distal resection margins^{10,11}. The introduction of stapling devices has facilitated this technique, permitting an even lower resection line without increases in local tumour recurrence¹⁰⁻¹². Local excision of low rectal cancer can be considered oncologically safe for small, low-risk tumours¹³ of Mason stage I or II¹⁴, because the probability of lymph node involvement for such lesions is less than the probability of postoperative mortality after a major resection¹⁵. The 'no touch' isolation technique introduced by Turnbull *et al.*¹⁶ was used in the present series whenever possible, as it has brought a significant increase in the survival rate and protects against intraoperative tumour dissemination. The oncological prognosis can be further improved by principal lymph node dissection, including the N₃ group¹⁷, by *en bloc* resection of infiltrated neighbouring organs, and by simultaneously resecting synchronous hepatic metastases¹⁸.

The data in this retrospective study were derived from a homogeneous surgical series without adjuvant therapy. The surgical procedures were standardized and no patient was lost to follow-up.

Patients and methods

Patients were operated on for colorectal cancer between 1 January 1984 and 31 December 1990. The mean age of the 276 patients with colonic carcinoma was 67 years, and that of the 299 patients with rectal carcinoma 65 years. The male:female ratio was 311:264.

One surgeon (G.J.) operated on 91 per cent of the patients. All resections were performed in the Lloyd-Davies position with a median laparotomy from the xiphoid to the symphysis pubis. The 'no touch' isolation technique¹⁶ was meticulously applied. Linear or circular stapling devices were used for all anastomoses. Protective colostomies were established only in cases of faecal contamination. Similarly, emergency procedures in the presence of acute bowel obstruction were always performed with radical intent, with the additional resection of the distended proximal colon and primary anastomosis. Lymph node dissection including the N₃ group was carried out in all patients. The marginal mucosa was always mechanically cleansed before anastomosis and thereafter the abdomen was thoroughly rinsed with distilled water. In cases of infiltration of adjacent structures or organs, an *en bloc* or monobloc resection was performed, where possible. Synchronous hepatic metastases were resected simultaneously whenever possible¹⁸.

For statistical analysis Student's *t* test and the χ^2 test were employed. Survival rates are cancer-specific, calculated using the actuarial method¹⁹. No patients were lost to follow-up. The term Dukes' 'D' was not included in the original Dukes' classification⁵ but was used for patients with stage IV TNM tumours.

Surgical procedure: colon

The surgical treatment of colorectal carcinoma requires an applied anatomy of the lymphatic system. It is necessary to remove not only

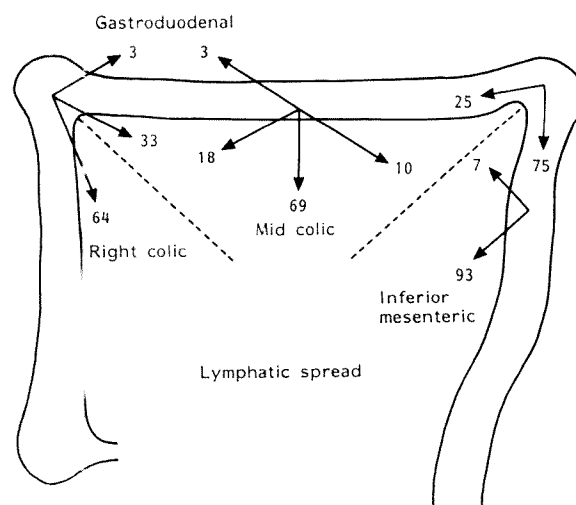


Figure 1 Incidence of infiltrated lymph nodes in different drainage zones. Values are percentages

Table 1 Surgical procedures for cancer of the colon

Tumour frequency (%)	Location	Procedure		
		Resection	Arteries ligated	Anastomosis
35.9	Tumour of caecum, ascending colon	Right hemicolectomy	Ileocolic, right colic	Ileotransverse
4.3	Advanced tumour (T ₃₋₄ /G ₃) of ascending colon, right flexure	Extended right hemicolectomy, excision of greater omentum	Ileocolic, right colic, mid colic, right gastroepiploic, gastrocolic	Ileum–descending colon
5.4	Tumour of transverse colon	Excision of transverse colon, greater omentum	Mid colic, right gastroepiploic, gastrocolic	Ascending–descending colon
1.8	Advanced tumour of transverse colon	Subtotal colectomy	Ileocolic, right colic, mid colic, right gastroepiploic, inferior mesenteric	Ileorectal
4.0	Advanced tumour of left flexure or descending colon	Excision of transverse and/or descending colon and/or sigmoid colon	Mid colic, inferior mesenteric	Ascending colon–rectum
48.6	Tumour of descending or sigmoid colon	Left hemicolectomy	Inferior mesenteric	Transverse colon–rectum

the tumour, but also all the draining lymphatic system. Resection of the adjacent lymph drainage zone was performed, in addition, for carcinomas near border zones (*Figure 1*). The surgical procedures, tumour location, depth of penetration and grading are shown in *Table 1*. As a rule, the major supplying vessels were ligated at their origin at either the aorta or the superior mesenteric artery.

Surgical procedure: rectum

Rectal cancer of the upper third was removed by anterior resection of the rectum, whereas low anterior resection was carried out for cancer of the middle third and for well or moderately differentiated cancer of the lower third. Small carcinomas of the lower third were treated by local excision, provided that they were well or moderately differentiated and mobile within the rectal wall. Poorly differentiated carcinomas of the lower third were treated by abdominoperineal resection. The sacral wound cavity after abdominoperineal resection was always tamponaded²⁰. Exact dissection along Waldeyer's and Denonvilliers' fascia was carried out in all major resections to allow complete removal of the mesorectum. As a rule the inferior mesenteric artery was ligated at its origin. The anastomosis of all left colorectal resections was protected against intraluminal pressure by a transanally inserted rectal tube²¹. In addition, to avoid diffuse peritonitis in the event of leakage, the anastomosis was separated from the abdominal cavity by suturing peritoneum or left-sided omentum over the sacral cavity; drainage was conducted laterally to avoid possible contamination of the peritoneal cavity.

Results

Colon

Curative resection was possible in 223 of the 276 patients (80.8 per cent). Tumour resection was carried out in 272 cases (98.6 per cent). Dukes' A tumours were diagnosed in 54 patients (19.6 per cent), Dukes' B in 80 (29.0 per cent), Dukes' C in 79 (28.6 per cent), and Dukes' 'D' in 63 (22.8 per cent). Tumour differentiation had a significant influence on the incidence of distant metastases and on survival (*Table 2*). Poorly differentiated tumours were associated with a higher rate of distant metastases ($P < 0.01$) and a lower 5-year patient survival rate ($P < 0.01$). In 28 patients resection was extended to include neighbouring lymph drainage zones. In ten of the 28 cases lymph vessel invasion was found on histopathological examination. In two cases lymph nodes in the neighbouring lymph drainage zone were tumour positive. Protective colostomies were necessary in only two patients (0.7 per cent). Complications after operation were observed in 18 cases (6.5 per cent), requiring relaparotomy in seven. Anastomotic leakage occurred in five cases (1.8 per cent). One of these patients died following diffuse peritonitis, one required no therapy, and three were treated adequately with a temporary colostomy. Altogether seven patients (2.5 per cent) died in the postoperative period (*Table 3*). Death was due to

Table 2 Tumour differentiation and its influence on incidence of distant metastases at time of operation and on patient survival

Differentiation	No. of patients*	Percentage with distant metastases	5-Year survival rate (%)†
Colon (n = 276)			
G ₁	28 (10.1)	14	84(11)
G ₂	211 (76.4)	21	69(4)
G ₃	36 (13.0)	36	31(10)
G ₄	1 (0.4)	—	—
Rectum (n = 299)			
G ₁	24 (8.0)	4	84(8)
G ₂	234 (78.3)	18	65(4)
G ₃	40 (13.4)	42	40(9)
G ₄	1 (0.3)	—	—

*Values in parentheses are percentages; †values in parentheses are s.e.

Table 3 Surgical procedure and postoperative hospital mortality rate

	No. of patients operated on	No. of deaths
Colon (n = 276)		
Curative	223	4 (1.8)
Palliative	53	3 (6)
Rectum (n = 299)		
Curative		
Anterior resection	62	3 (5)
Low anterior resection	113	3 (2.7)
Abdominoperineal resection	72	1 (1)
Local excision	9	0 (0)
Palliative		
Resection	22	2 (9)
Abdominoperineal resection	12	0 (0)
Other	9	1 (11)

Values in parentheses are percentages

cardiorespiratory complications in four cases, urological complications in two patients and anastomotic leakage in one. There was no death after extended resection. Locoregional tumour recurrence occurred in six (4.0 per cent) of the patients operated on for cure between 1 January 1984 and 31 December 1988 with a mean follow-up of 44 months. No local recurrence was observed in patients with extended resection. The 5-year tumour-specific survival rate(s.e.) for patients operated on for cure was 81(4) per cent. Survival related to tumour stage is illustrated in *Figure 2*.

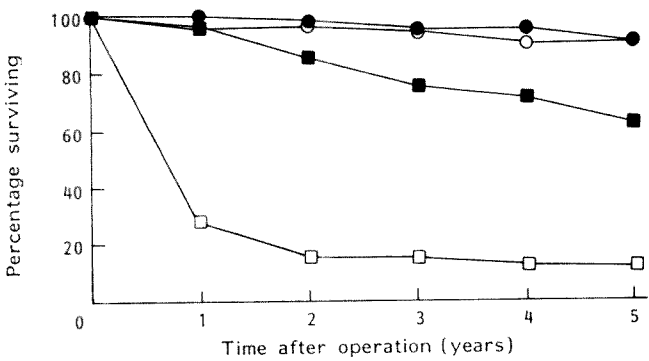


Figure 2 Tumour-specific survival curves of patients with colonic carcinoma according to tumour stage. ●, Dukes' A; ○, Dukes' B; ■, Dukes' C; □, Dukes' D

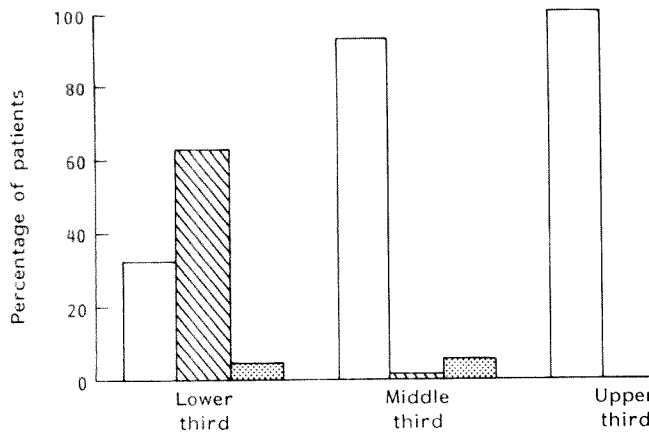


Figure 3 Surgical procedure for rectal carcinoma according to localization. □, Anterior resection; ▨, abdominoperineal resection; ▤, local excision

Table 4 Comparison of abdominoperineal resection and anterior resection of the lower third of the rectum

	Abdominoperineal resection (n = 69)	Anterior resection (n = 36)	P
Stage (I:II:III:IV)	20:23:20:6	11:11:12:2	—
Grading (G ₁ :G ₂ :G ₃)	6:54:9	1:33:2*	—
Locoregional recurrence (%)†	14.3	10.5	n.s.
Distant recurrence (%)†	20.0	10.5	n.s.
5-Year survival rate (%)	52	90	<0.01

*An anterior resection was performed for two Dukes' A lesions (G₃); †minimum observation period 2 years. n.s., Not significant (χ^2 test)

Rectum

Curative resection was possible in 256 of the 299 patients (85.6 per cent). Tumour resection was possible in 295 cases (98.7 per cent). The influence of tumour differentiation on the incidence of distant metastases and on survival is shown in Table 2. Dukes' A tumours were diagnosed in 74 patients (24.7 per cent), Dukes' B in 76 (25.4 per cent), Dukes' C in 87 (29.1 per cent) and Dukes' D in 62 (20.7 per cent). Figure 3 illustrates the surgical procedure according to tumour location. A comparison of abdominoperineal resection and anterior resection of the lower third of the rectum is shown in Table 4. For anterior resection the 5-year survival rate was significantly higher than for abdominoperineal resection of the lower third. A protective colostomy was established in 12 (6.1 per cent) of the 197 patients with primary anastomosis. Complications after operation were observed in 37 of the 299 patients (12.4 per cent); relaparotomy was necessary in seven of these cases. Inadequate anastomosis was noted in 19 cases

Table 5 Rectal locoregional tumour recurrence and patient survival rate according to tumour location and surgical procedure

	Proportion affected (%)	Tumour recurrence rate (%)	5-Year survival rate (%)
Tumour location			
Lower third	42.8	12.3(3.8)	65(6)
Middle third	27.1	16.9(4.9)	71(7)
Upper third	30.1	10.9(4.2)	82(5)
Surgical procedure*			
Abdominoperineal resection	24.1	16.0(5.2)	49(9)
Anterior resection	20.7	10.6(4.5)	79(6)
Low anterior resection	37.8	14.6(3.9)	76(6)

Values in parentheses are s.e. *Other procedures (palliative, local excision) undergone by 17.4 per cent

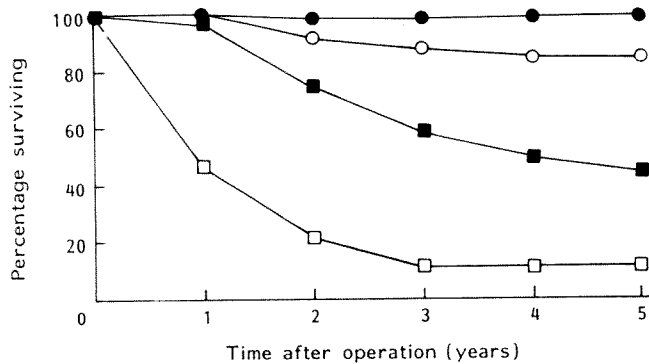


Figure 4 Tumour-specific survival curves of patients with rectal carcinoma according to tumour stage. ●, Dukes' A; ○, Dukes' B; ■, Dukes' C; □, Dukes' D

(10.3 per cent). The rate of anastomotic leakage was significantly higher ($P < 0.05$) for low anterior resection (14.2 per cent) than for anterior resection (4.8 per cent). No patient died from anastomotic leakage. Death after operation occurred in ten (3.3 per cent) of all surgically treated patients (Table 3). Locoregional tumour recurrence occurred in 25 (13.4 per cent) of the patients operated on for cure between 1 January and 31 December 1988, with a mean follow-up of 42 months. There were no statistically significant differences in recurrence rates with respect to tumour location or resection technique (Table 5). Of the 113 patients undergoing low anterior resection, 17 had a distal microscopically tumour-free margin of < 2 cm. The incidence of local recurrence in these patients, 11.8 per cent with a mean follow-up of 28 months, was not statistically higher than that for patients with other tumour locations or resection techniques (Table 5). Patients who had undergone only local excision were all free of recurrence after a mean follow-up of 52 months (at 1 January 1991). The 5-year tumour-specific survival rate(s.e.) for patients operated on for cure was 71(4) per cent. Survival rates according to tumour location and resection technique are shown in Table 5, and according to tumour stage in Figure 4. Survival rates were higher for anterior and low anterior resection than for abdominoperineal resection ($P < 0.05$).

Discussion

Early diagnosis is essential in achieving better results for colorectal cancer. The patient survival rates and good prognosis associated with early stages are clearly demonstrated in this study. Almost 50 per cent of the patients had Dukes' A or B tumours and this would appear to be an essential factor in increasing the overall survival rate for colorectal cancer.

The evaluation of surgery for colorectal cancer has to take into consideration anastomotic leakage, postoperative deaths, local recurrence and survival rates. Leakage of the anastomosis

is a major complication and therefore one of the most frequent causes of death after operation²². In this study leakage of a colonic anastomosis was observed in only 1.8 per cent of patients. Leakage of a rectal anastomosis was more frequent (10.3 per cent) but there was no case of diffuse peritonitis and so formal relaparotomy was never necessary; no patient died after rectal anastomotic leakage. We believe that the careful drainage of the rectal anastomosis, which lies outside the peritoneal cavity, is an important factor in avoiding diffuse peritonitis. Tamponade of the sacral cavity after abdominoperineal resection often reduces local septic complications²⁰. The mortality rate after operation in this series, 2.5 per cent for colonic carcinoma and 3.3 per cent for rectal cancer, is relatively low compared with values in the literature²³⁻²⁶.

The incidence of local recurrence reflects the radical nature of the surgery. The local recurrence rates of 4.0 and 13.4 per cent in this series after colonic and rectal surgery, respectively, are comparatively low^{25,27-30}. The benefit of an extended resection margin for colonic carcinoma is obvious only for the two patients with positive nodes in the neighbouring drainage zones, which otherwise would have remained. For the ten patients with lymph vessel invasion no benefit for extended resection can be proved, but the possibility of its preventing local recurrence cannot be ruled out. The low recurrence rate for patients undergoing extended resection may not be representative owing to the small number of such cases, but the present results do support this approach.

By resecting whole lymph drainage zones the histopathological staging, especially for Dukes' B and C tumours, is also more accurate. The incidence of Dukes' C tumours (28.9 per cent) in this study corresponds to that of other reports³¹. Lymph node-positive patients would be expected to benefit most from radical surgery, as shown by the 5-year patient survival rates of 62 per cent for the colon and 44 per cent for the rectum (Dukes' C). These results confirm that a lymph drainage zone of a tumour, when infiltrated, should be graded as a localized rather than as a generalized stage³².

Recurrence rates for rectal carcinoma in this study confirm other reports^{33,34} that high sphincter-saving resection rates may be achieved for cancer in the lower third of the rectum, without increasing tumour recurrence. Even in patients with distal margins of <2 cm, there was no increase in tumour recurrence. It is interesting that resection in the lower third carries a better prognosis than abdominoperineal resection. As the recurrence rate for abdominoperineal resection was slightly higher (but not significantly so), one can explain this discrepancy only through a negative selection for abdominoperineal resection (Table 4). Poorly differentiated tumours in the lower third were treated with an abdominoperineal resection because of the possibility of submucosal spread. If the mesorectum is radically resected high local recurrence rates may be avoided, but the high incidence of distant metastases of poorly differentiated tumours appears to be a limiting factor. Furthermore, patients selected for abdominoperineal resection tend to have bulky tumours, often invading the anal sphincters. A comparison between abdominoperineal resection and low anterior resection is, therefore, not appropriate; the mere selection of abdominoperineal resection reflects a worse prognosis.

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Haemorrhoids are associated not with hypertrophy of the internal anal sphincter, but with hypertension of the anal cushions

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A combined manometric and ultrasonographic study of the internal anal sphincter was carried out in 20 patients with haemorrhoids and 20 age-matched normal controls. Mean(s.e.m.) basal anal pressure was significantly higher in patients than in controls, 62(4) versus 45(6) cmH₂O (P < 0.05), although there were no significant differences in mean maximum basal and squeeze pressures. During rectal distension 90 per cent of patients showed no reduction in anal pressure in the outermost anal channel, although the internal sphincter electromyogram was suppressed and the external sphincter electromyogram did not necessarily increase above baseline. The mean(s.e.m.) maximum residual pressure was significantly higher in patients, 70(6) versus 45(6) cmH₂O (P < 0.05). Direct pressure measurement in anal cushions exhibited abnormally high median pressure in patients compared with controls, 35 versus 10 cmH₂O (P < 0.001). Pressures recorded during coughing and straining were also significantly higher in patients than in controls (P < 0.001). Ultrasonographic study of the anal canal revealed a clear image of the internal sphincter, the thickness of which could easily be measured. The mean(s.e.m.) thickness of the sphincter was not significantly different, 2.3(0.2) versus 2.1(0.1) mm, between patients with haemorrhoids and controls (P = 0.18). The absence of any significant differences in the internal sphincter thickness between normal subjects and patients with haemorrhoids suggests that the high anal pressure in patients with haemorrhoids is of vascular origin.

High anal pressure is a common feature of patients with haemorrhoids, and is often thought to be caused by increased activity of the internal anal sphincter (IAS)¹⁻³. This theory is supported by the finding of ultraslow waves during anal manometry in such patients, and the observation that anal pressure is reduced after forcible anal dilatation^{3,4}. An alternative hypothesis proposes that the pressure in the anal cushions themselves may be responsible for the high anal pressures in patients with haemorrhoids⁵. This would explain why haemorrhoidectomy has been found to reduce anal pressure⁶.

Recently Kamm and colleagues⁷ described a family of patients who had constipation and abnormally high anal pressure associated with genetically determined hypertrophy of the IAS. In the present study endoscopic ultrasonography was performed to measure the thickness of the IAS in patients with haemorrhoids to test whether the IAS is hypertrophic in this condition. Results have been compared with measurements of pressures in the anal canal and the vascular cushions.

Patients and methods

Patients and controls

Studies were carried out in 20 men with first-degree haemorrhoids of mean age 43 (range 30-60) years. Seventeen of these patients were referred because of rectal bleeding after defaecation; none complained of anal pain. Twenty age-matched men with no history of anorectal disease and no abnormality at proctoscopy were studied as normal controls. All subjects gave written informed consent to the study and the protocol was approved by the ethical subcommittee of the Sheffield Health Authority.

Ultrasonographic measurement of the IAS was carried out usually on the same day that the diagnosis of first-degree haemorrhoids was

made. Standard anorectal manometry and direct measurement of pressure in anal cushions were conducted within 1 week of diagnosis.

Combined manometry and electromyography

The detailed methods and protocol used have been described previously⁸. The anorectal pressures at multiple sites were measured using a 7-Fr polyvinyl tube bearing an inflatable balloon. The electrical activities of the IAS and external anal sphincter (EAS) were recorded at the same time by means of a bipolar electrode inserted into the superficial EAS or into the intersphincteric groove between the superficial EAS and the IAS. The independent functions of the EAS and IAS were studied under basal conditions and during intermittent rectal distension. The electrical activity of the EAS was semiquantified as the percentage of that recorded during maximum sphincter contraction.

Direct measurement of pressures in the anal cushions

Pressures in the anal cushions were measured with subjects in the left lateral position using a 25-Fr spinal needle perfused with 5 per cent glucose at 3 ml h⁻¹ and connected to a pressure transducer⁶. A slit proctoscope was inserted into the anal canal to abolish the contribution of sphincter muscle contraction to intravascular pressure.

Ultrasonographic scanning

With the subject in the supine position, a Brüel and Kjær (Nærum, Denmark) 7.5-MHz rotating ultrasonographic scanner of outer diameter 1 cm was inserted just inside the anal margin. The subject was asked to relax as much as possible. The IAS showed as a distinct, hypoechoic circular ring in relation to mucosa, submucosa and longitudinal muscle (Figure 1). Cross-sectional images were obtained at several sites in the anal canal and the IAS was measured at its maximum thickness. The mean value of the thickness of the IAS at this particular section was calculated from measurements made at eight equidistant points around the anal canal.



Figure 1 Ultrasonographic image of the anus in a normal subject. The structures of the anus and its adjacent tissues can be seen easily

Table 1 Anorectal pressures and electrical activity of the external anal sphincter during rest, rectal distension and straining in patients with haemorrhoids and normal controls

	Controls (n = 20)	Patients (n = 20)	P
Minimum basal pressure (cmH ₂ O)	45(6)	62(4)	<0.05
Squeeze pressure (cmH ₂ O)	280(12)	281(15)	n.s.
Maximum residual pressure during rectal distension (cmH ₂ O)	45(6)	70(6)	<0.05
Electrical activity of EAS during 100 ml distension*	58(7)	58(8)	n.s.

Values are mean(s.e.m.). *Expressed as a percentage of that observed during maximum squeeze. EAS, external anal sphincter; n.s., not significant

Statistical analysis

The statistical significance of the differences in the anorectal pressures was assessed using analysis of variance⁸. Data obtained from direct pressure measurements in anal cushions and from ultrasonographic studies were analysed using the Mann-Whitney *U* test. The χ^2 test was used to assess differences between groups.

Results

Anorectal manometry

The minimum basal pressures at all anal ports were significantly higher in patients with haemorrhoids than in controls ($P < 0.05$), although the squeeze pressure was not significantly different from that of controls (Table 1). During balloon distension, controls showed anal pressure reduction in all ports, but 18 patients had no anal relaxation in the outermost anal channel, and five showed no reduction at any site in the anal channel with a distending volume up to 100 ml. This occurred despite suppression of the electrical oscillation of the IAS activity; often there was no or only a transient increase in activity of the EAS (Figure 2). The maximum residual anal pressure recorded during rectal distension was higher ($P < 0.05$) in patients than in controls (Table 1).

Pressure measurement in anal cushions

The basal pressure and pressure recorded during coughing and straining were significantly higher ($P < 0.001$) in patients than in controls (Table 2).

Ultrasonographic measurement of internal anal sphincter thickness

There were no significant differences between patients and

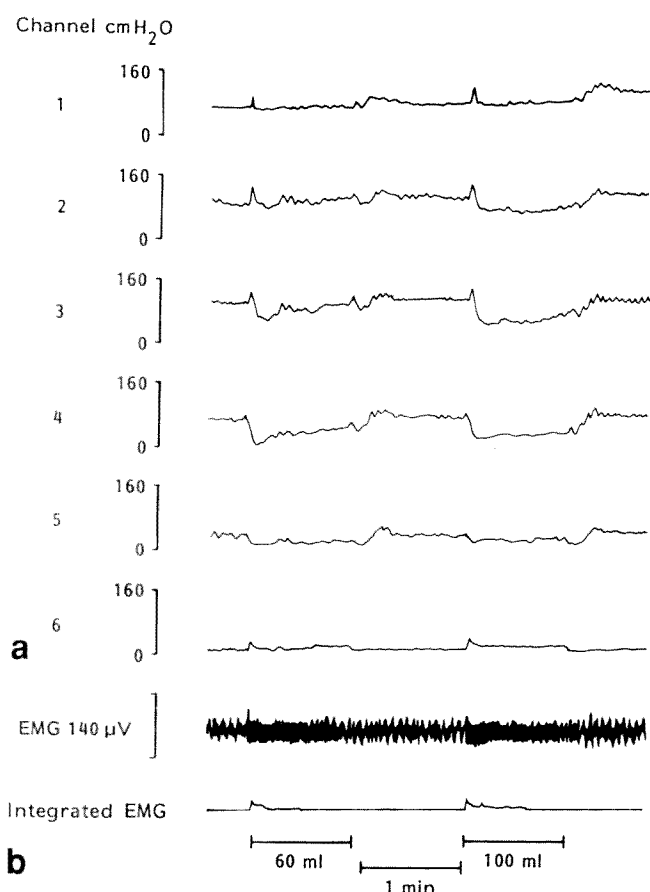


Figure 2 Recording of **a** anorectal pressure and **b** electrical activity as an electromyogram (EMG) of the external anal sphincter and internal anal sphincter (IAS) before, during and after inflation of a rectal balloon with 60 and 100 ml air in a patient with non-prolapsing haemorrhoids. Channels 1–6 represent ports situated 0.5, 1.0, 1.5, 2.0, 2.5 and 4.5 cm from the anal margin. Note that there was no anal relaxation in the outermost channels during the balloon distension, although the electrical oscillation of the IAS appeared suppressed

Table 2 Pressures in the anal cushions in patients with haemorrhoids and normal controls

	Controls (n = 20)	Patients (n = 20)	P*
Basal pressure (cmH ₂ O)	10 (0–25)	35 (20–80)	<0.001
Pressure during coughing (cmH ₂ O)	30 (10–50)	60 (30–80)	<0.001
Pressure during straining (cmH ₂ O)	55 (40–80)	80 (45–90)	<0.001

Values are median (range). *Mann-Whitney *U* test

controls in the mean(s.e.m.) values of the eight circumferential measurements of the thickness of the IAS, 2.3(0.2) versus 2.1(0.1) mm ($P = 0.18$). There was no significant correlation between IAS thickness and minimum basal pressure ($r = 0.34$, $P > 0.05$).

Discussion

This study confirmed that the high basal pressure in patients with first-degree haemorrhoids was related to an increase in pressure in the vascular cushions. This might explain why the pressure remained high, particularly in the outermost aspect of the sphincter, during rectal distension, despite the fact that the IAS relaxes and the EAS activity is not necessarily higher than predistension values⁵. However, no study using direct measurement of IAS tone is available and it is still possible that

increased activity in the IAS might contribute to high anal pressure and to the pathogenesis of haemorrhoids.

The present study extends previous work by measuring the width of the IAS by endoscopic ultrasonography. There was no significant difference in IAS thickness between patients with haemorrhoids and controls. This strengthens the hypothesis that the high pressures in patients with haemorrhoids are probably caused by hypertensive anal cushions.

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Paper accepted 4 December 1991

Correspondence

Quantitative measure of small vessel anastomotic contour using corrosion resin cast models

Sir

I read with interest the article by Messrs John, Hornick, Rees and Edmondson (*Br J Surg* 1991; **78**: 1384–5). The necessity for technical precision in vascular anastomosis is of vital importance and the principal of anastomotic casts as an aid to surgical training is obviously desirable. There are, however, some aspects of the described methodology that might limit its usefulness.

I have attempted similar studies using epoxy resins, which I found very difficult to handle. Fortunately I discovered a cheap, 'user-friendly' alternative. Dow Corning make a white bath and kitchen seal (silicone rubber) ideal for the purpose. It is sold in syringe-like containers, cures relatively quickly, gives off no heat and is not compromised by moisture. It is possible to pressurize the cast using a small volume (<0.5 ml) of water at the tip of a needle introduced at some convenient point, connected to a three-way tap, pressure manometer and fluid reservoir. The resulting cast is rubbery and durable. It is not necessary to use any dissolution techniques to remove the tissues from the cast as they can be easily cut away without damaging the cast. Analysis of cross-sectional detail is easy because the silicone rubber can be cut with an ordinary scalpel blade.

I was impressed by the technique described for reading anastomotic contour. I am concerned, however, that the equipment and time involved might not be universally available. It is widely accepted that the anastomotic regions of primary importance are the heel and toe. I suggest, therefore, that measurement at each of these is sufficient to illustrate a trainee's progress. All that is required is to measure the artery in question in two planes; dividing one diameter by the other results in a 'distortion quotient'. Any deviation from 1.0 (a perfect circle) indicates anastomotic distortion.

I have used the above technique to compare the anastomotic distortion incurred by direct expanded polytetrafluoroethylene-artery, Miller collar and Taylor patch anastomoses¹.

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1. Tyrrell MR, Chester JF, Vipond MN, Clarke GH, Taylor RS, Wolfe JHN. Experimental evidence to support the use of interposition vein collars/patches in distal PTFE anastomoses. *Eur J Vasc Surg* 1990; **4**: 95–101.

Authors' reply

Sir

I am grateful for Mr Tyrrell's ingenious suggestion for making vascular models. It is true that handling epoxy resin can be difficult initially but after experience with the technique we have found it relatively straightforward to use. Although the technique we described for measuring the contour takes time, it does allow a very accurate measure. My concern with Mr Tyrrell's suggestion is the accuracy of his technique. The degree of distortion, e.g. from contraction within anatomical structures, is known to be very small for epoxy resins. As far as I am aware this fact is not known for silicone rubber. In addition, as the cast is 'rubbery', direct measurement of diameter by a micrometer device will be susceptible to inaccuracies from distortion.

I agree that the silicone rubber technique would provide valuable information regarding major distortion, particularly at the toe or heel of an anastomosis, but I question whether the accuracy of the technique would allow measurement of more subtle changes which may be relevant to the surgeon in training.

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Laser-assisted laparoscopic excision of liver cyst

Sir

We read with interest the recent article by Paterson-Brown and Garden on the surgical management of symptomatic benign hepatic cysts (*Br J Surg* 1991; **78**: 1047).

We would agree that laparoscopic excision of the cyst roof appears to offer an advantage to the patient in terms of postoperative recovery when compared with traditional laparotomy. However, our recent experience with a case similar to that described by Paterson-Brown and Garden suggests that this can be successfully accomplished without the necessity for laser dissection.

A 63-year-old woman was referred with a 12-cm symptomatic cyst in the right lobe of the liver identified on computed tomography; infective causes were excluded. Under general anaesthesia, the laparoscope was introduced through a 10-mm cannula inserted through a subumbilical incision and a thick-walled cyst was identified on the anterolateral aspect of the right hepatic lobe. One 5-mm cannula was inserted in the right subcostal region and a second 5-mm cannula was passed into the peritoneal cavity in the epigastrium immediately to the right of the falciform ligament. The cyst contents were aspirated, and then using a combination of a diathermy hook and scissors, the roof of the cyst was excised and submitted for histological examination. Blood loss was minimal and at the end of the procedure a closed suction drain was inserted through the epigastric cannula and manipulated into the cavity of the cyst. The patient made a rapid and uncomplicated recovery and was discharged home on the third day after operation. Histological examination confirmed the benign nature of the cyst.

The scope of laparoscopic surgery continues to expand, aided by ongoing technological developments. In these days of financial constraint, however, our experience serves to illustrate that, as for laparoscopic cholecystectomy, the availability of a laser is not an essential prerequisite for safe laparoscopic surgery. Adequate dissection and safe haemostasis can be achieved using a combination of scissor excision and conventional diathermy. The omission of a laser represents a significant capital saving, and this may be important to many centres aiming to establish a laparoscopic service.

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Identification of bile duct stones in patients undergoing laparoscopic cholecystectomy

Letter 1

Sir

The recent article by Joyce *et al.* (*Br J Surg* 1991; **78**: 1174–6) was an interesting paper which addressed one of the more important problems facing surgeons who perform laparoscopic cholecystectomy, namely the management of bile duct stones. The arguments against routine operative cholangiography during cholecystectomy are well known¹ but are even more compelling when cholecystectomy is performed laparoscopically because the discovery of asymptomatic bile duct stones in this situation would probably not be regarded as an indication for conversion to open cholecystectomy². The authors' suggestion that operative cholangiography may be helpful in patients with difficult anatomy is not supported by the fact that their single bile duct injury occurred in a patient who had had a normal operative cholangiogram.

Ideally, patients with significant bile duct stones should be identified before operation; the authors chose to do this by subjecting all patients to intravenous cholangiography (IVC). However, they point out that all patients found to have duct stones had abnormal liver biochemistry and it has previously been shown that abnormal liver function or a

Correspondence

history of jaundice or pancreatitis are all reliable indicators of bile duct stones³. Furthermore, the authors demonstrate that endoscopic retrograde cholangiopancreatography (ERCP) is a more accurate way of detecting duct stones than either IVC or ultrasonography and perform ERCP and endoscopic sphincterotomy on all patients with bile duct stones before operation. Do they therefore now intend to abandon IVC altogether and instead carry out ERCP on all patients with abnormal liver function tests or a history of jaundice or pancreatitis? It would appear from their figures that such a policy would have resulted in eight additional ERCP investigations but would have saved 100 intravenous cholangiograms and up to 60 operative cholangiograms.

A. D. N. Scott

Professorial Surgical Unit
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1. Pernthaler H, Sandbichler P, Schmid Th, Margraiter R. Operative cholangiography in elective cholecystectomy. *Br J Surg* 1990; **77**: 399–400.
2. Scott ADN, Greville AC, McMillan L, Wellwood JMcK. Laser laparoscopic cholecystectomy – the results of the technique in 210 patients. *Ann R Coll Surg Engl* (in press).
3. Hauer-Jensen M, Karsen R, Nygaard K *et al*. Consequences of routine preoperative cholangiography during cholecystectomy for gallstone disease: a prospective, randomised study. *World J Surg* 1986; **10**: 996–1002.

Authors' reply

Sir

We are grateful for the interest shown by Mr Scott in our paper and would like to address some of the issues raised by him. We would first disagree with his comment that 'The discovery of asymptomatic bile duct stones ... would probably not be regarded as an indication for conversion to open cholecystectomy'. The natural history of asymptomatic ductal stones is unknown, and factors such as stone size, duct calibre etc. which can all be deduced from an operative cholangiogram must be considered before they can be dismissed as being unimportant.

It is true that our one presumed bile duct injury occurred in the presence of a normal operative cholangiogram. However, we have found operative cholangiography very useful in delineating the anatomy in some of our more difficult laparoscopic cholecystectomies.

All of our patients with proven duct stones had abnormal liver biochemistry but an equal number of patients with abnormal liver function tests did not have duct stones detected on intravenous or operative cholangiography.

It is incorrect to suggest that we are advocating abandoning intravenous cholangiography (IVC) and liberalizing our indications for endoscopic retrograde cholangiopancreatography (ERCP). ERCP has an essential diagnostic and therapeutic role in patients considered for laparoscopic cholecystectomy; its widespread use, of course, should not occur as there are significant risks and a high failure rate associated with it. Our study was taken to assess the value of IVC in identifying ductal stones before operation and to compare it with operative cholangiography. This, we believe, we have adequately shown. We therefore suggest that operative cholangiography should be reserved for selective use provided that the bile duct has been adequately imaged before operation and attention is directed to the clinical and biochemical indicators of bile duct stones.

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T. J. Egan
P. V. Delaney
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Letter 2

Sir

We were interested to read the recent report from Joyce *et al.* (*Br J Surg* 1991 **78**: 1174–6) advocating the use of intravenous cholangiography (IVC) before laparoscopic cholecystectomy as an alternative to intraoperative cholangiography.

Their findings support those of Huddy and Southam¹, who found that IVC and operative cholangiography are equally reliable at detecting common bile duct (CBD) stones. Huddy and Southam also pointed out that using preoperative IVC instead of operative cholangiography would reduce operating time, provide advance knowledge of biliary anatomy, and allow better planning of the operative procedure. Many surgeons have employed selective operative cholangiography with traditional open cholecystectomy when historical, biochemical or ultrasonographic findings suggest the presence of CBD stones. Since March 1991 we have employed selective preoperative IVC in association with laparoscopic cholecystectomy according to the same criteria.

We have reviewed our last 100 cholecystectomies, of which 74 were performed laparoscopically. Twenty-six were planned as open procedures during this early phase of our experience with laparoscopic techniques because of anticipated difficulties (previous upper abdominal incision or an acutely inflamed gallbladder) or because CBD stones were strongly suspected (clinical jaundice or recent pancreatitis). CBD stones were present in ten of the 100 patients. Six of those undergoing open cholecystectomy had CBD stones identified on operative cholangiography and proceeded to duct exploration. Two patients who were jaundiced and two others whose stones were identified by preoperative IVC underwent endoscopic retrograde cholangiopancreatography (ERCP) and duct clearance before proceeding to laparoscopic cholecystectomy.

Preoperative IVC was performed selectively in 22 cases on the basis of subclinical abnormalities of liver function tests (bilirubin > 17 $\mu\text{mol/l}$, alkaline phosphatase > 199 units/l, alanine transaminase > 40 units/l) or a CBD > 7 mm in diameter on ultrasonography. Five of the 22 cases undergoing IVC had evidence of CBD stones and therefore proceeded to ERCP. Stones were identified and cleared in two patients, while three others were found to have clear duct systems with evidence that stones had recently passed. The remaining 17 cases had normal ducts on IVC and have therefore been able to avoid unnecessary ERCP.

None of the patients has developed clinical features of retained CBD stones after a median follow-up of 5 months. We are pleased with the quality of IVC and, as yet, have recorded no adverse reactions apart from one patient who reported nausea on infusion of contrast. On the basis of these early results, we intend to continue with our policy of using selective preoperative IVC in preference to operative cholangiography. Further follow-up and repeated auditing of our results will be required before the long-term effects of this policy become known.

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1. Huddy SPJ, Southam J. Is intravenous cholangiography an alternative to the routine pre-operative cholangiogram? *Postgrad Med J* 1989; **65**: 896–9.

Book reviews

Adult and Pediatric Urology. Vols I and II. 2nd ed.

J. Y. Gillenwater, J. T. Grayhack, S. S. Howards and J. W. Duckett. 286 × 226 mm. Pp. 2366. 1991. USA: Mosby Year-Book.

The second edition of this major multiauthor textbook attempts to cover all current urological practice and has been produced only 4 years after the first edition, an indication of the rapid advances that are being made in this field. This book competes in an area where there are already several major volumes on urological surgery but admirably fulfils its role as a reference, both for those in training and those in senior posts. It is very thorough in its coverage and most of the chapters, including the preclinical ones (in many texts the most difficult to understand), are comprehensive in content and are written in a style that is easy to read. Overlap in subjects covered between chapters is uncommon. However, it is disappointing to find chapters in which references do not appear to have been updated since the first edition; an example is Chapter 41, on the scrotum and testis, in which I could identify no reference more recent than 1985. This is despite the rapidly evolving and prolific literature covering testicular oncology during that period. Only a few of the chapters I looked at had more than three or four new and updated references, although in contrast the chapter on urinary tract infection had about 20 new references and that on benign prostatic hypertrophy included some published in 1990.

While none of the chapters was particularly weak, some were gems of pathophysiological insight, such as those on voiding function and dysfunction. The chapter on prostate cancer was another good example, including not only a wealth of material but also applying arguments in favour of and against various treatments. This was done on the basis of rational argument, using the literature as a guide, rather than proclaiming the standard therapeutic options often based on little more than traditional practice. The Authors even included data from this side of the Atlantic.

I found the contents page rather poor; the chapters are not clearly highlighted and initially I missed this page and skipped over it, which is a shame because it is an important part of a book and reflects on the entirety, particularly as it is often read first. Despite the difficulty inherent in producing a multiauthor volume of this size and complexity, the Editors have succeeded in achieving their aims of covering evenly and in depth the wide spectrum of urological abnormalities and the options for managing them. With the onset of compulsory tertiary examinations such as the FRCS Urology on our doorstep and the introduction of European Association Board exams in 1992, comprehensive textbooks like this are going to be increasingly in demand. These volumes would grace any library as a reference text and as such I would recommend them wholeheartedly.

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Thoracic Outlet Syndrome: a Common Sequela of Neck Injuries

R. J. Saunders. 263 × 186 mm. Pp. 348 + xx. Illustrated. 1991. Philadelphia: Lippincott. £75.

The thoracic outlet syndrome (TOS), which embraces a confusing spectrum of clinical presentations, stimulates debate and often a conflict of views that reflect a lack of awareness of its true nature. This volume not only illuminates an ill-understood concept of the TOS but also focuses on the even more confounding area of TOS following neck injury. A detailed, conscientious and critical analysis of virtually the entire literature on TOS is summarized, drawing on the Author's own extensive experience in managing patients with the syndrome, a substantial number of whom give a history of associated trauma.

The opening chapters trace the history, dating from the recognition of the cervical rib 250 years ago into the modern era of the TOS, and examine the controversies surrounding the aetiology and management of this condition. The relevant underlying anatomy and pathophysiology are elucidated including the complex anomalous spatial inter-relationships of locomotor, vascular and nerve structures, and the manner in which they may be altered as a consequence of injury. Particular reference is made to original research work on the cytoarchitecture and histochemistry of the scalene muscles which may be damaged following closed neck injuries.

The key features of the history, symptoms, physical findings and diagnostic criteria in the Author's own series are analysed objectively against a background of published evidence in a way that is very helpful to the clinician. Interestingly, while arterial TOS and venous TOS are well known, neurogenic TOS, especially in those patients for whom there is a lack of objective data, is not generally recognized. The entire gamut of differential and associated diagnoses involving locomotor and neurovascular structures of the neck, shoulder girdle and upper limb are described.

The limitations of available diagnostic techniques and the liability of some of these to misinterpretation emphasizes the reliance which must be placed on careful evaluation of subjective information and detection of physical signs. Clearly stated diagnostic criteria, goals of treatment, and the therapeutic options available, both conservative and surgical, underline the Author's experience in managing TOS. The indications for surgery, the correct choice of operation, and the ideal operative approach, complemented by clear diagrams, are given sufficient space in the book; pertinent practical points and arguments are often restated for maximal impact. The parameters influencing the outcome of anterior scalenotomy, first rib resection and reoperation for TOS are distilled from the literature and from the Author's data in the form of numerous tabulated summaries that provide a useful yardstick for the practising surgeon. Chapters dedicated solely to recurrent TOS, arterial TOS and venous TOS, assisted by algorithms of management, and an overview of the key points separating speculation and hypothesis from fact, all make good reading.

'Whiplash' injuries, the medicolegal implications of which have acquired a certain notoriety, particularly in relation to TOS, are discussed. Sound advice is offered on the assessment of disability, prognostication of outcome while litigation is pending, and presentation of professional evidence in court.

The book represents a unique, richly referenced, definitive and authoritative work, the product of dedicated years of commitment to the study and treatment of patients with TOS. For those who wish to delve further into the subject, the Author has diligently provided a 60-page bibliography of chronologically listed references, each with an annotated synopsis. The pleasure of reading the book is enhanced by the methodical layout of the chapters, the clear subheadings and the helpful illustrations. The contents should be of great interest to general, vascular and orthopaedic surgeons, neurosurgeons, neurologists and practitioners in physical medicine.

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Atlas of Anal Endosonography

C. I. Bartram and S. J. D. Burnett. 257 × 193 mm. Pp. 124 + ix. Illustrated. 1991. Oxford: Butterworth-Heinemann. £35.

Anal ultrasonography is a relatively new technique which is undoubtedly going to be of increasing use to the coloproctologist. The technique is simply performed as an outpatient procedure with little or no discomfort. This atlas represents the state of the art with regard to the technique of anal endosonography. It contains chapters and illustrations related to the normal anatomy of the anal canal, the basic principles of ultrasonography, traumatic lesions of the anal sphincters, fistula and anal sepsis, idiopathic incontinence and miscellaneous conditions. The text describes well the technique, instrumentation, methodology and interpretation of the images. The illustrations are well produced and are complemented by adjacent line drawings for clarification. Anal ultrasonography is at present in a continuing state of development and the authors include an addendum related to recent research which has further clarified the position regarding the interpretation of the external anal sphincter.

This atlas will undoubtedly be useful for surgeons and radiologists with an interest in anal surgery who wish to benefit from the experience that Drs Bartram and Burnett have accumulated at St Mark's.

J. Beynon

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Notices and announcements

28 June–3 July 1992

4th Oxbridge Organ Transplantation Course

Cambridge, UK

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

29 June–3 July 1992

Practical Nutritional Support – Third Annual Training Course for Clinicians

Southampton, UK

Information: Mr Brendan Moran, Department of Human Nutrition, University of Southampton, Southampton SO9 3TU, UK

2–3 July 1992

Surgical Research Society Meeting

Edinburgh, UK

Information: Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

2–3 July 1992

Atherosclerotic Renal Artery Stenosis

London, UK

Information: Mr G. Hamilton, University Department of Surgery, Royal Free Hospital School of Medicine, London NW3 2QG, UK

5–10 July 1992

Immunology and the Nervous System: Clinical Aspects

Oxford, UK

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

6–10 July 1992

European School of Oncology Course on Colorectal Cancer

Lake Orta, Italy

Information: Secretariat, European School of Oncology, Via Venezian 18, 20133 Milan, Italy

10–11 July 1992

Hong Kong Surgical Forum – Summer 1992

Hong Kong

Information: Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

10–12 July 1992

Minimally Invasive Medicine – From Diagnosis to Therapy

Berlin, Germany

Information: KIT Marketing Services GmbH, Behrenstraße 23, D-1080 Berlin-Mitte, Germany

13–17 July 1992

Annual Diagnostic Imaging Seminar

Martha's Vineyard Island, Massachusetts, USA

Information: Nancy Fedullo, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, USA

16–18 July 1992

XVIIth International Update on Liver Disease

London, UK

Information: Professor Neil McIntyre, University Department of Medicine, Foyal Free Hospital, London NW3 2QG, UK

22–24 July 1992

British Association of Paediatric Surgeons XXXIX Annual International Congress

Leeds, UK

Information: Secretariat (BAPS), Bell Howe Conferences, 1 Willoughby Street, Beeston, Nottingham NG9 2LT, UK

2–4 September 1992

Ultrasound Angiography '92

Southampton, UK

Information: Secretariat, Ultrasound Angiography '92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK

9–11 September 1992

2nd Nottingham International Breast Cancer Meeting

Nottingham, UK

Information: Mrs Wendy Bartlam, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

20–23 September 1992

VIIIth Edmondo Malan International Day of Surgery – Endo-laparoscopic and Mini-invasive Surgery

Parma, Italy

Information: Professor Gian Carlo Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14 43100 Parma, Italy

20–24 September 1992

Combined Meeting of the Association of Surgeons of Great Britain and Ireland and Trinity College Dublin Quatercentenary Meeting

Dublin, Ireland

Information: Mr T. N. Walsh, Department of Surgery, St James's Hospital, Dublin, Ireland

22–24 September 1992

Fifth Meeting of the International Association of Pancreatologists

Athens, Greece

Information: Congress Secretariat, Dr C. Arvanitakis, First Medical Department, University of Thessaloniki, AHEPA General Hospital, 54 006 Thessaloniki, Greece

24–26 September 1992

Postgraduate Course – Principles of Colon and Rectal Surgery

Minnesota, Minneapolis, USA

Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue Southeast, Minneapolis, Minnesota 55414, USA

7–8 October 1992

VIIth National Conference of the Association of Paediatric Surgeons of Pakistan

Lahore, Pakistan

Information: Dr Z. B. Attar, Department of Paediatric Surgery, National Institute of Child Health, Karachi, Pakistan

8–9 October 1992

Second GI Tract Laparoscopic Surgery International Meeting

Liège, Belgium

Information: Catherine Marissiaux, Clinique St-Joseph, Chirurgie de l'Appareil Digestif, Rue de Hesbaye 75, B-4000 Liège, Belgium

15–16 October 1992

European School of Oncology 10th Anniversary Events

Milan, Italy

Information: European School of Oncology, Via Venezian 18, 20133 Milan, Italy

27 October–4 November 1992

Anaesthesia and Surgical Intensive Care: Controversies and Conflicts

Bristol, UK

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

2–6 November 1992

Specialist Short Courses: Advanced Surgical Techniques

London, UK

Information: Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

6–7 November 1992

International College of Surgeons 38th Annual Meeting of the Japan Section – 'Controversies in Surgery'

Tokyo, Japan

Information: Professor K. Kimura, Department of Surgery, Tokyo Medical College, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan 160

15–18 November 1992

Update and Future Trends in Fibrin Sealing in Surgical and Non-surgical Fields

Vienna, Austria

Information: Univ. Prof. G. Schlag, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstraße 13, A-1200 Vienna, Austria

15–21 November 1992

Advances in Cancer Treatment

London, UK

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

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The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401-5 or the *Annals of Internal Medicine* 1988; **108**: 258-65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

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Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600-1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

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The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

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The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

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Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5.7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for

Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or ¹⁻³. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184-6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer-Verlag, 1981: 123-63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782-4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the ' $\pm$ ' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

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There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the *P* value. For example, ' $t = 1.34$, 16 d.f., $P = 0.20$ ' might be reported. Actual *P* values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

New books for the General Surgeon...

Atlas of Anal Endosonography

Clive Bartram MB BS MRCP FRCP

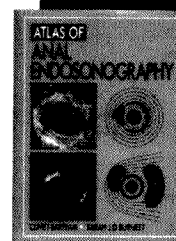
Consultant Radiologist, St Mark's Hospital, London, UK

Sarah J D Burnett

Senior Registrar in Radiology, St Mark's Hospital, London, UK

This atlas assumes no prior knowledge of the technique of anal endosonography. Sufficient detail is provided to allow those without formal training the means of examining and interpreting sonographs.

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M M Henry MB FRCS

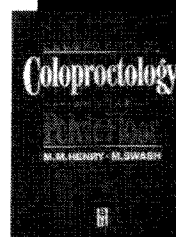
Consultant Surgeon, Central Middlesex Hospital,

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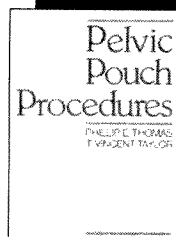
Research Fellow and Surgical Registrar, University Department of Surgery, Manchester Royal Infirmary, UK

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Consultant Surgeon, University Department of Surgery, Manchester Royal Infirmary, UK

A state-of-the-art review of spincter-saving surgery in the treatment of patients with diseases of the colon. The procedure involves the formation of a pouch from parts of the small bowel, which then acts as a reservoir or neorectum.

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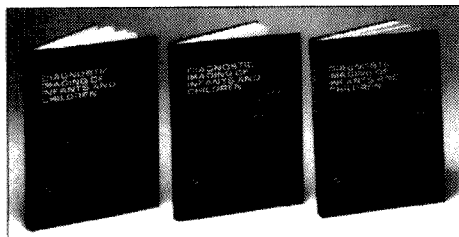
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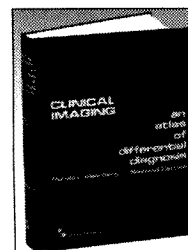
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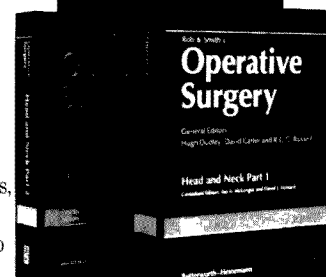
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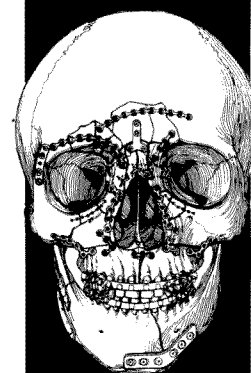
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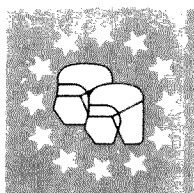
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Eurosurgery '92, held in Brussels, 2–5 June 1992, establishes Eurochirurgie for the first time as a truly Pan-European Congress, bringing together without exception all 28 countries of Europe. Eurochirurgie now includes the Scandinavian nations and countries of Eastern Europe. Soon we hope to welcome the states emerging from the old USSR.

In parallel with this expansion, the organization of Eurochirurgie has been formalized. Recently the statutes were approved by all participating societies. Eurochirurgie is proud to have established a permanent link with *The British Journal of Surgery* for publication of the best abstracts of the oral and poster presentations from the Congress. These abstracts were chosen by an international scientific committee of 135 surgeons covering every specialty. This association with *The British Journal of Surgery* will extend to publication of a selection of the presentations at the meeting as full papers. These articles will be grouped together in a special issue of the Journal early in 1993.

The first abstract supplement bears witness to the strength and quality of European surgery. Nevertheless, these abstracts are only a small part of the entire programme of the Second European Congress of Eurochirurgie. The full programme includes European sessions, organized by Eurochirurgie, national sessions organized by participating societies and symposia presented by the local organizing committee in Belgium. These reviews and symposia complement the presentation of original material in the free paper sessions, and ensure that all subjects of interest to every specialist in surgery will be covered at the meeting.

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Eurosurgery '93, London, 14–17 September 1993;

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The Editors of this supplement and the Eurochirurgie Permanent Committee welcome you to this Congress in Brussels and look forward to your participation in future.

Gerard Champault
Supplement Editor
Secretary General Eurochirurgie

Acquired immune deficiency syndrome

Current status and risk factors of human immunodeficiency virus infection

D. Salmon, *Hôpital Claude Bernard Bichat, Paris, France*

In December 1991, worldwide, a total of 9–10 million adults and almost one million children born from infected mothers has been infected with human immunodeficiency virus (HIV). The highest prevalence is in sub-Saharan Africa (six million infected adults), followed by the Americas (two million), south and south-east Asia (over one million) and western Europe (half a million). Of these, over one and a half million have already progressed to acquired immune deficiency syndrome (AIDS), with an average of 10 years between HIV infection and AIDS. In Europe, the highest prevalence is recorded in Switzerland, followed by France (20 000 cumulative AIDS cases of whom 51 per cent are dead).

Because of the reduction in high-risk behaviour among homosexuals and drug abusers in developed countries, worldwide transmission is now attributable, in 75 per cent of cases, to heterosexual contact. The male:female ratio is close to one in developing countries, and is around four but decreasing in the USA and Europe.

Future projections show that there will be a tripling of present cases by the year 2000. The annual incidence will probably continue to decrease in developed countries after a peak in the mid-1980s, but will increase in Africa, Latin America and particularly in Asia, where infection has spread recently but where it is expected to exceed the prevalence of infection in Africa in the late 1990s. This pandemic already has demographic consequences in Africa where one-third of sexually active adults are infected in many urban areas.

Reliability of surgical biopsy and fine needle aspiration in human immunodeficiency virus-positive patients with lymphadenopathy

J.M. Argüello, A.J. Torres, J.M. García-Asenjo, V. Roca, L. Díez-Valladares and J.L. Balibrea, *II Cátedra de Cirugía, Hospital Universitario 'San Carlos', Madrid, Spain*

The aim of this study was to evaluate the usefulness of surgical biopsy (SB) and fine needle aspiration (FNA) in the pathological diagnosis of lymphadenopathy associated with human immunodeficiency virus (HIV) infection.

We have performed 52 SB and 30 FNA on 64 HIV-positive patients, all of whom suffered from persistent generalized lymphadenopathy with some other manifestation (fever, weight loss, etc.). The most frequent risk factor was intravenous drug abuse. The analysis of the study was retrospective for SB and prospective for FNA. In the first 16 patients submitted to FNA, SB was also performed to confirm pathological findings.

SB achieved a diagnostic reliability of 44 per cent (16 of 36 patients comprising ten cases of mycobacterial lymphadenitis, three of Kaposi's sarcoma, two of non-Hodgkin's lymphoma and one of Hodgkin's lymphoma). Reliability for FNA was 33 per cent (ten of 30 patients, comprising six cases of mycobacterial lymphadenitis, one of leishmaniasis, one of Hodgkin's lymphoma and two of Kaposi's sarcoma). In the first 16 patients in which SB + FNA was performed there were three false negatives for mycobacterial lymphadenitis. Sensitivity for FNA in these 16 patients was 100 per cent in tumour disease. The complication rate for SB was 22.2 per cent and 0 for FNA.

Considering the high diagnostic reliability and the absence of complications in lymphadenopathy, pathological diagnosis in selected HIV patients can be achieved by FNA as the first diagnostic step, reserving SB for those cases in which FNA does not give a definitive diagnosis.

Abdominal emergency surgery on human immunodeficiency virus-positive patients

H. Johanet, J.P. Marmuse, K. Mourad, J.Y. Le Goff and G. Benhamou, *Department of General and Digestive Surgery, Bichat-Claude Bernard Hospital, Paris, France*

From May 1983 to March 1991, we performed 88 emergency laparotomies on 73 human immunodeficiency virus (HIV)-positive

patients. The indications, pathology and operative mortality in this population are described.

There were 62 men and 11 women of median age 35.9 (range 21–68) years. Risk factors were sexual in 46 cases, drug abuse in 16 cases and transfusions in two cases; in 12 patients these factors were not determined, and three patients had multiple risk factors. HIV was discovered in 12 patients at the time of operation and it was already known in 61 cases (from 1 to 71 months). Of the 73 patients, 78 per cent were operated on for an HIV-related condition and 75 per cent fulfilled the diagnostic criteria for AIDS.

In 34 patients there was a known preoperative diagnosis: appendicitis (18), cholecystitis (nine) or miscellaneous (seven), with a hospital mortality rate of 21 per cent.

Of 39 patients operated on for exploratory laparotomy, in 12 cases this was for organ syndrome failure, in nine for sepsis with peritoneal irritation, in seven for trauma, in six for occlusion and in five for miscellaneous conditions, with a hospital mortality rate of 59 per cent.

The overall mortality rate was 53 per cent for the first 36 patients, and 30 per cent for the last 37.

Indications for cholecystectomy in patients with acquired immune deficiency syndrome

P.H. Cugnenc, P. Wind, A. Berger, C. Drevillon, P. Frileux and J.-P. Barbier*, *Service de Chirurgie Digestive and *Service de Gastro-Entérologie, Hôpital Laennec, 42 rue de Sèvres, 75007 Paris, France*

Patients with acquired immune deficiency syndrome (AIDS) may develop acalculous cholecystitis causing abdominal pain which is relieved by cholecystectomy; the majority also have associated cholangitis. The relative clinical importance of cholecystitis and cholangitis is uncertain. Consequently, the indications for surgery are poorly defined. The aim of this study was to determine the indications for surgery.

Since 1985, 21 patients with AIDS were admitted with hepatobiliary manifestations and thickened gallbladder on ultrasonography. Eight patients (seven men and one woman, age range 32–58 years) underwent cholecystectomy with the clinical and ultrasonographic diagnosis of acute cholecystitis. All had abdominal pain, fever greater than 38.5°C, and weight loss greater than 10 per cent body-weight. Four patients had an elevated serum alkaline phosphatase. All had a thickened gallbladder wall on ultrasonography (5–12 mm) and two had gallstones. Four had cholangitis confirmed by cholangiography.

Indications for surgery were persisting symptoms and abdominal signs, with progressive deterioration of the patient's general condition, despite 20–180 days of antibiotic treatment. Four patients had septic shock at the time of surgery. Biochemical and ultrasonographic findings remained unchanged from the onset of symptoms to the time of surgery. One patient died immediately after surgery. Abdominal pain and sepsis resolved in all the remaining patients. Two died 20 days after surgery because of other manifestations of AIDS. Five died 6, 9, 10, 12 and 14 months after operation because of AIDS. Two suffered recurrent symptomatic cholangitis.

In conclusion, acalculous cholecystitis is a cause of abdominal pain and sepsis in patients with AIDS, and is relieved by cholecystectomy. The indications for surgery are purely clinical. Recurrent symptoms are usually due to progressive cholangitis. Cholecystectomy should be considered in patients with AIDS suffering severe persisting symptoms of hepatobiliary disease.

Thoracic surgery in patients with acquired immune deficiency syndrome

J. Mouroux, D. Benchimol, C. Rotomondo, P. Hoffman, E. Bernard, B. Padovani and H. Richelme, *Service de Chirurgie Thoracique, Hôpital Pasteur, Nice, France*

The aim of this retrospective study was to determine the reasons for and the results of surgical thoracic procedures in human immunodeficiency virus (HIV)-infected patients.

From 1987 to 1991, 30 patients with proven HIV infection underwent a diagnostic and/or therapeutic thoracic operation: 25 men and five women with a mean age of 33.7 (range 24–50) years. Diseases encountered included – *Pleural diseases*: 12 patients with pyogenic empyema (in nine of whom this was secondary to pneumonia) treated by decortication; five patients with pneumothorax, all secondary to *Pneumocystis carinii* pneumonia (two of whom had bilateral pneumothorax, and one with associated pneumomediastinum) treated by pleurodesis. *Pulmonary diseases*: two lung cancers, two lung abscesses, one localized tuberculosis treated by resection (lobectomy or segmentectomy); in four cases, open lung biopsy allowed a diagnosis of lymphoma (two cases), toxoplasmosis or Kaposi's sarcoma. *Mediastinal diseases*: three tuberculosis, one *Mycobacterium avium* infection were diagnosed by lymph node biopsy by mediastinoscopy.

Five patients died within 9 days of operation (mortality rate: 17 per cent), all from acquired immune deficiency syndrome (AIDS)-related diseases, as proved at autopsy. One patient developed a wound infection. The remaining 24 patients had an uneventful postoperative recovery.

At follow-up, 14 patients were alive 2–41 months after operation. Ten patients died 4–39 months after operation, all from AIDS-related diseases, and one patient was lost to follow-up.

It is concluded that surgical thoracic procedures can be safely and effectively performed when necessary for diagnosis or treatment in AIDS-related thoracic diseases.

Anorectal pathology and acquired immune deficiency syndrome

R. Cope and J.M. Debou, *Gouin Hospital, Clichy, France*

Anorectal lesions in patients carrying the human immunodeficiency virus (HIV) are uncommon (13 per cent). While Kaposi's sarcoma is 20 000 times more common in patients with acquired immune deficiency syndrome than in the general population and carcinoma of the anal canal is also more common in HIV-positive homosexual males, other anorectal lesions encountered in proctology are not specific.

Nevertheless, the weeping and extensive nature of certain anal ulcerations, as well as erythematous or eczematous lesions of the margin of the anus caused by chronic diarrhoea, should lead to suspicion of HIV infection. When the anus is affected by sexually transmitted disease (condyloma acuminata, syphilis, herpes) routine HIV serology should be requested, and especially in the following circumstances: (1) florid papillomatosis or extensive herpetic lesions refractory to standard treatment; (2) explosive syphilis with generalized cutaneomucosal manifestations and significant systemic manifestations; and (3) lymphogranuloma inguinale, although this is rare in our experience. History indicating sexual habits (homosexuality, promiscuous heterosexuality, anal intercourse, as well as the existence of chronic diarrhoea, and full physical examination seeking enlarged lymph nodes, are all factors to be taken into consideration in support of the diagnosis.

Apart from painful emergencies justifying immediate surgery (thrombosed prolapsed haemorrhoid, painful fissure and, above all, acute suppuration), indications for surgery should consider the patient's general condition, the stage of the disease and expected benefits in terms of patient comfort. Finally, possible problems of delayed postoperative healing should not limit indications for surgery.

Malignant tumours, haemopathies and acquired immune deficiency syndrome

A. Bourgeon, P. Dujardin, D. Benchimol, B. Taillan and H. Richelme, *Université de Nice-Sophia Antipolis, Hôpital Pasteur, Service de Chirurgie Abdominale et Thoracique, Nice, France*

Approximately 25 per cent of patients infected with human immunodeficiency virus (HIV) ultimately develop neoplastic disease; Kaposi's sarcoma is the initial manifestation in 20 per cent. This neoplasm is associated exclusively with sexually transmitted acquired immune deficiency syndrome (homosexual and heterosexual) and may occur at any stage of immunodepression. Although for a long time localized to the skin and mucosae, Kaposi's sarcoma frequently spreads to the viscera. These lesions tend to remain asymptomatic,

although thoracic involvement may result in fatal respiratory insufficiency.

Malignant non-Hodgkin's lymphoma (immunoblastic, large cell, Burkitt's and cerebral lymphomas) develop in 4 per cent of patients infected with HIV regardless of the mode of contamination (this incidence appears higher than in the general population). Although several studies have reported a rise in the frequency of these lymphomas, with increased survival, they can occur regardless of immune status. The clinical picture is characterized by the high frequency of diffuse disease (grades III and IV) from the outset, aberrant localizations, and an aggressive course. Disease onset may be sudden and include neurological, respiratory and gastrointestinal complications, and compressive phenomena. Once the acute disease phase has passed, patients with such lymphomas can be managed by the same therapeutic regimens as patients not infected by HIV, provided that their immune status and performance status are adequate.

In addition to those neoplasms defined as stage IVd of the Atlanta CDC classification, other neoplastic diseases also appear associated with HIV infection. Hodgkin's disease appears to be the most frequent (based on European studies of grade IV drug abusers); the highly symptomatic disseminated nature of the disease from the outset is a common feature. Solid squamous cell tumours of the head and neck and anal region have been reported in younger patients, with different risks from non-infected subjects. Testicular tumour also appears to be more frequent in drug abusers. Finally, various neoplasms have been reported, although no correlation has been established with HIV infection. These cancers are unusual in that they occur in younger subjects without the classic risk factors associated with the neoplasm in question, and feature both a more severe clinical presentation and a more aggressive course.

Acquired immune deficiency syndrome in the operating room: the risk for the surgeon and team

F. Marchal, G. Champault and D. Cooley, *Texas Heart Institute, Houston, Texas, USA*

In 1992 the target population of the human immunodeficiency virus (HIV) is not strictly limited to the population at risk such as homosexuals, drug addicts, multitransfused subjects or some socioethnic groups. Thus, the surgeon will have to deal more frequently with HIV-positive patients. Surgical personnel are at risk for HIV infection, primarily as a result of sustaining injuries with sharp instruments that are contaminated with blood or body fluid. To a lesser extent, they are also at risk from contact of blood with their skin or mucous membranes, especially if the skin is abraded, injured or afflicted with dermatitis. It appears essential for the surgical team to evaluate this risk by knowledge of the patient's serostatus. Should this test be mandatory?

The evaluation process is discussed with regard to the epidemiology of the virus and the type of procedure being performed. Universal precautions are to be taken by all healthcare workers. These are extensively detailed with the emphasis on the work in the operating theatre such as double gloving, special gowning, avoiding any hand-to-hand transfer of sharp instruments, using stapling instruments rather than needle suturing, etc. Most of the questions related to what a healthcare worker should do if he is a victim of an operative injury (needlestick, scalpel injury, etc.) are answered with respect to ethical problems, the confidentiality of the serostatus of the source patient and of the healthcare worker, the efficacy of the prophylactic treatment by zidovudine (AZT), and the associated risk of other blood-borne pathogens such as hepatitis B virus. A better knowledge of the real risk of the surgical contamination from the patient to the healthcare worker or vice versa will contribute to improved mutual confidence.

Routine preoperative screening for human immunodeficiency virus in a general surgery department

S. Evrard, K. van Haaften, M. Vix, D. Christmann* and J. Marescaux, *Departments of Surgery and *Infectious Diseases, Hôpital Civil, Strasbourg, France*

Human immunodeficiency virus (HIV) is no longer confined to high-risk groups because of a considerable risk of heterosexual contamination. A systematic preoperative screening for HIV

Acquired immune deficiency syndrome

seropositivity was performed in order to evaluate the risk of contamination for surgical staff.

Between May 1989 and August 1991, prospective and consecutive screening was performed on every patient with unknown HIV serology admitted to our unit. All patients with AIDS operated on during this period were excluded from the study. The enzyme-linked immunosorbent assay (ELISA) technique was used and all seropositivity was confirmed by the Western blot test. The seropositive patients were operated on with precautions such as double gloves, goggles and impervious disposable clothing.

Of 4119 serologies performed, three were positive and two were doubtful, giving a rate of infection of 7/10 000 for this population. All the positive patients belonged to a high-risk group. After surgery they were followed up by the Department of Infectious Diseases.

With a prevalence of 7/10 000 our population is at low risk. According to Hussain *et al.*¹ the risk of accidental injuries to surgeons during operation is 5.6 per cent. The risk of HIV infection after skin puncture with infective materials is 1 per cent according to Bradbeer². So the risk of contamination for a surgeon for one procedure in our series was 35/10⁸. This percentage corresponds to an estimated range between 1/13 × 10⁸ and 1/450 000 (Reference 3). During his career a surgeon will perform about 35 000 surgical acts, so the cumulative risk of contamination in our experience is about 1 per cent. Living in a low risk area we did not see an increase in prevalence but we have to take account of this increase in our calculation of the cumulative risk of contamination during the following years. Being already 1 per cent and still increasing, this risk is considerable. The patients' rights are high level medical care and protection by medical confidentiality. Is it not a fundamental right for a surgeon to protect himself and his family by knowing his patients' serology?

1. Hussain SA, Latif ABA, Choudhary AAAA. Risk to surgeons: a survey of accidental injuries during operations. *Br J Surg* 1988; 75: 314-16.
2. Bradbeer C. AIDS epidemiology and screening. *Med Intern* 1986; 2: 1241-6.
3. Hagen MD, Meyer KB, Pauker SG. Routine preoperative screening for HIV: does the risk to the surgeon outweigh the risk to the patient? *JAMA* 1988; 259: 1357-9.

Lymph node biopsy in patients with acquired immune deficiency syndrome

R. Moreno, P. Fernández, F. García, J. Madrid, J. Suárez, L. Aseñsio, H. Urquijo and L. García-Sancho, *Cirugía General, Hospital La Paz, Madrid, Spain*

The aim of this study was to determine the clinical value of lymph node biopsy in human immunodeficiency virus (HIV)-positive patients.

Cf 116 lymph node biopsies performed in this surgery service, 38 (32.8 per cent) were performed on HIV-positive patients with persistent generalized lymphadenopathy (nine women and 29 men, mean age 25 years). All nodes were taken under local anaesthesia and sent in saline to the pathology department.

Twenty of the nodes (53 per cent) demonstrated follicular hyperplasia; five (13 per cent) revealed follicular depletion; in six (16 per cent) *Mycobacterium tuberculosis* was cultured; two (5 per cent) showed Hodgkin's lymphoma; one patient (3 per cent) showed

syphilitic adenitis, and in four (11 per cent) patients no abnormality was found.

Lymph node biopsy performed in HIV-positive patients is useful to exclude associated disease. It is important to determine the histological patterns for prognosis. However, the biopsy cannot confirm HIV infection, even if the alterations in nodes may be due to the direct action of the virus.

Role of splenectomy in human immunodeficiency virus-related thrombocytopenia

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The mechanism of thrombocytopenia in patients with human immunodeficiency virus (HIV) remains unknown, being possibly the result of increased obstruction in the spleen. Splenectomy could be an effective treatment. Thirty HIV-positive patients with thrombocytopenia who have undergone splenectomy have been prospectively followed, with a mean follow-up of 41 months, to evaluate the safety and efficacy of splenectomy. There were no perioperative deaths and the morbidity rate was low. Persistent complete response was found in 21 patients, six patients had a partial response and remained asymptomatic. Only three patients showed no response. Three patients developed acquired immune deficiency syndrome during follow-up, which was no different from the expected incidence.

Splenectomy is a safe and effective treatment for severe, symptomatic, AZT-resistant thrombocytopenia purpura.

Vascular surgery in patients with acquired immune deficiency syndrome

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From November 1989 to November 1991, five patients with acquired immune deficiency syndrome (AIDS) were operated on for life-threatening arterial conditions requiring vascular surgery.

Three patients had a mycotic aneurysm of the abdominal aorta, two ruptured and one fissured at time of diagnosis. Vascular procedures included resection of the aneurysm and *in situ* graft reconstruction. Bacteriological cultures were positive, with *Salmonella enteritidis* (one case), *Haemophilus influenzae* (one) and *Mycobacterium tuberculosis* (one). The postoperative course was uneventful and all three patients are alive and without evidence of opportunistic infection or recurrence of the aneurysm at a mean follow-up time of 1 year. Therefore, vascular surgery seems to be justified in patients with AIDS without evidence of opportunistic infection other than at the arterial site.

In contrast, two other patients had synchronous opportunistic infection at the time of vascular surgery. In one case, a resection bypass was performed for an iliac artery aneurysm. The patient died after 15 days from a *Pneumocystis carinii* infection. In the other case, an elective femoropopliteal bypass graft became infected early after operation by *Staphylococcus aureus* and subsequently ruptured. Direct manual compression of the groin during transfer to the operating room exposed all medical personnel to massive human immunodeficiency virus contamination. Therefore, in patients with AIDS with opportunistic infection synchronous to vascular conditions requiring surgery, the risk of collective contamination must be carefully balanced against the patient's prognosis.

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Better diagnosis of suspected acute appendicitis: a prospective model

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More than 300 000 appendicectomies are performed annually in France, three to four times as many as in other European countries or the USA. As the prevalence of appendicitis is not higher in France, it must be assumed that French surgeons remove more healthy or non-inflamed appendices than fellow surgeons.

Of 1824 cases of appendicectomy in our abdominal pain databank, there were no cases of appendicular abscess or peritonitis in patients whose temperature was $<38^{\circ}\text{C}$, who had no abdominal guarding and whose leucocyte count was $<10\,000\text{ ml}^{-1}$. If these criteria were met the rate of acute appendicitis dropped from 26.7 to 11.8 per cent, the rate of normal appendices rose from 17.2 to 28.0 per cent, and the diagnosis of non-specific pain rose from 12 to 20 per cent.

We tested this model prospectively to determine whether it was safe to manage patients with these three findings conservatively. Of 499 patients with right iliac fossa tenderness seen between November 1988 and January 1989, 54 met all three criteria. Of 26 of these patients discharged from the hospital, only one returned with recurrent pain, and underwent appendicectomy, but had a non-inflamed appendix. Twenty-eight patients were operated on: eight had non-inflamed appendices; in 17 inflammation was limited to the mucosa or the submucosal layers; and three patients had inflammation of the muscular or serosal layers. During this time, 353 patients underwent appendicectomy: 35 per cent had acute transmural appendicitis, 39 per cent had inflammation limited to the submucosal layer, and 23 per cent had non-inflamed appendices.

In conclusion, if one admits that acute inflammation of the appendix limited to the submucosal layer does not necessarily require surgery, many unwarranted appendicectomies may be avoided by observing patients whose temperature does not exceed 38°C , whose abdomen remains soft, and whose white blood count does not exceed $10\,000\text{ ml}^{-1}$. Under these conditions, the risk of severe appendicitis is nil, and that of observing acute appendicitis is 5.5 per cent.

Ultrasonography in suspected acute appendicitis

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Ultrasonography in suspected acute appendicitis has been shown to enhance diagnostic accuracy, at least if performed by expert ultrasonographers. This study was designed to assess the diagnostic accuracy and clinical impact in suspected appendicitis of routine ultrasonography, performed by six surgical residents.

The clinical course of 669 unselected patients admitted with suspected appendicitis was studied prospectively. Clinical and ultrasonographic findings were recorded in a standardized fashion and correlated with laparotomy findings and pathological outcome in 171 patients (143 cases with proven acute appendicitis; prevalence, 21.4 per cent) and clinical as well as follow-up data in the remainder.

The overall sensitivity, specificity and accuracy of the clinical diagnoses of appendicitis were 50.3, 95.1 and 85.5 per cent, respectively (positive predictive value (PPV) 73.5 per cent; negative predictive value (NPV) 87.6 per cent); those for ultrasonography were 79.2, 96.8 and 92.9 per cent (PPV, 87.0 per cent; NPV 94.4 per cent).

The combined approach of clinical classification and routine ultrasonography improved the diagnostic accuracy in suspected acute appendicitis with percentages as follows: sensitivity, 84.7; specificity, 96.3; accuracy, 93.8; PPV, 86.5; NPV, 95.8; the rate of unnecessary laparotomies was reduced to 10.5 per cent.

Ultrasonographic evaluation of patients with suspected acute appendicitis, when performed by ultrasonographically trained surgeons, is highly reliable and is considered to be of great assistance in surgical practice.

Time of operation and diagnosis in patients with suspected appendicitis

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The aim of this study was to relate the high incidence of healthy appendices to the time of laparotomy and to ascertain whether there is an indication for other diagnostic tools such as ultrasonography to lower the frequency of unnecessary appendicectomies.

The study group consisted of 377 consecutive adult patients who underwent surgery for suspected acute appendicitis. The onset of symptoms and time of surgery was registered in all patients.

A total of 284 patients (75.3 per cent) had acute appendicitis on histological examination. The diagnostic accuracy at night and in the early hours of the morning (between 24.00 and 08.00 hours) was 78 per cent of the 82 operated patients. From 08.00 to 17.00 hours 151 were operated on and 76 per cent had appendicitis. Finally from 17.00 to 24.00 hours, 73 per cent had appendicitis. The onset of symptoms was significantly lower at night compared with during the day. The perforated appendices were equally spread during the 24 h.

In conclusion, the diagnostic accuracy is slightly higher during the night when patients with shorter duration of symptoms undergo surgery. The reason for this might be that during the night patients with typical clinical signs of appendicitis are operated on, but during the day we are more liberal with our indications for laparotomy. There is need for better diagnostic accuracy during the later hours of the day when unnecessary surgery is performed.

Right iliac fossa pain: the value of paraclinical examinations in diagnosing acute appendicitis

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The aim of this prospective study was to evaluate the usefulness of the paraclinical examinations routinely used to confirm the preoperative diagnosis of appendicitis.

From 1 November 1989 to 1 December 1990, 102 patients (48 women, 54 men; mean age 22 years) were admitted urgently for pain in the right iliac fossa. After the standard physical examination, appendicitis was diagnosed in 25 cases, suspected in 56 and ruled out in 21. Following laboratory tests, plain abdominal radiography and ultrasonography, 73 cases (72 per cent) were considered to suffer from acute appendicitis and underwent a standard surgical procedure. Histologically, only 50 true inflammations of the appendix were confirmed. Laparotomy revealed no abnormality in 17 patients and various other diagnoses were found in six cases. Twenty-nine patients were kept under observation and did not finally undergo operation. Appendicitis remains above all a clinical diagnosis. The physical examination, however, tends to underestimate the reality, permitting a correct diagnosis which in only one of two cases is histologically confirmed. Among the blood tests, only a white cell count above $10 \times 10^9\text{ litre}^{-1}$ and a lymphocyte:leucocyte ratio below 0.20 proved significant in making the diagnosis of appendicitis.

The plain abdominal radiograph was never helpful. The sensitivity of abdominal ultrasonography was low (<20 per cent); however, the specificity was very high (>97 per cent). Therefore ultrasonography may confirm the clinical diagnosis of appendicitis and can also exclude other causes, particularly those of a gynaecological nature.

Laparoscopy should certainly soon find its place in the investigation of right iliac fossa pain with no precise diagnosis.

Laparoscopic diagnosis of right lower quadrant pain in women to avoid unnecessary appendicectomy

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Appendicectomy of a normal appendix is performed in about 10–30 per cent of cases. Removal of a normal appendix could be followed

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by immediate and long-term complications. The differential diagnosis of right lower quadrant (RLQ) pain is less of a problem in men than in women. This work aims to evaluate laparoscopy for making the right diagnosis of RLQ pain in women, thus avoiding unnecessary appendicectomy.

From May 1990 to October 1991, 68 women with acute RLQ pain were treated in our institution. The median age was 26 (range 15–50) years. An ultrasonographic examination was performed in women older than 30 years with uncertain assessment (eight cases). Ectopic pregnancies were excluded.

The patients were placed in three groups according to clinical diagnosis: group A: diagnosis of acute appendicitis (46 cases); group B: doubtful gynaecological disease with acute appendicitis (15 cases); group C: gynaecological disease (seven cases). After laparoscopic examination, a normal macroscopic appendix was not removed when gynaecological disease was evident.

In 23 cases (34 per cent), an unnecessary appendicectomy was prevented on the basis of laparoscopic findings (see Table).

Preoperative diagnosis	Laparoscopic diagnosis			
	Appendicitis	Mesenteric adenitis	Non-specific abdominal pain	Gynaecological disease
Group A	26	8	8	4
Group B	1	1		13
Group C	1			6

We conclude that the usefulness of laparoscopy in the diagnosis of appendicitis in women in doubtful cases seems to be confirmed and in our series decreases the unnecessary appendicectomy rate.

Appendicectomy by laparoscopy

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The recent development of laparoscopic surgery has drawn our attention to its use in cases of appendicitis, as recommended since 1983 by Semm. Here, we describe our results over the first 3 years of practising appendicectomy by this method.

From June 1988 to October 1991 we operated on 100 patients (45 men and 55 women) with an average age of 27.9 (range 9–75) years, all suspected of having acute appendicitis.

The appendix was catarrhal in 53 cases, suppurative in 36, gangrenous in eight, and one case of perforation was recorded. There were two cases of right iliac fossa guarding. Within the peritoneum there were six cases of loculated abscess, six cases of localized peritonitis and four of generalized peritonitis.

In nine patients, a laparotomy was performed; in six of these this was due to difficulty with the dissection, one was due to haemorrhage, one was due to necrosis of the appendicular base and one was due to technical reasons. There was no mortality. Four complications were observed. There were two cases of mild parietal suppuration; one case of more severe suppuration required hospitalization and antibiotic therapy; and one patient suffered recurrent pain on the fifth day after operation.

In summary, appendicectomy by laparoscopy is possible in the majority of cases, especially where the appendix is in an unusual position, the abdominal wall is thickened and where there is a severe peritoneal reaction. Generally, postoperative care is uncomplicated and comfortable for the patients. The procedure has become all the more feasible with increasing experience on the part of the operator.

New method of precision appendicectomy

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A new method of precision appendicectomy is described. The choice of place and length of the incision of the abdominal wall is performed with the use of special measuring equipment. The operative access is completed by insertion into the operative wound of a special isolator, providing prophylaxis of wound infection, and fixation of the vermiform appendix and caecum in the wound aperture. If necessary, capture of the intestine wall is performed with special forceps, which increase the degree of fixation with a reduction in trauma to the bowel. The appendix is captured and isolated with special clamps. The whole operation is performed at the level of the base of the appendix but the stump is practically absent, which preserves the contour of the caecum and decreases trauma. The abdominal wall wound is closed with the use of a collagen preparation, which provides better apposition of the sutures, decreasing the risk of inflammation and accelerating healing of the wound. The skin is closed with an intradermal suture with glue cover. If drainage of the abdominal cavity through the main incision is necessary, a new method with the application of a demountable pouch suture on the wound round the drainage and filling of the wound canal with collagencous sponge after removal of the drain is applied.

Precision appendicectomy has been applied to 360 patients with acute appendicitis: 150 had catarrhal appendicitis, 140 had a phlegmonous form, and 70 a gangrenous form. The wounds closed with primary healing in 100 per cent of cases. On draining the abdominal cavity through the main wound according to our method with the application of collagen preparations, closure of the wound was noted in 98.5 per cent of cases. There were no deaths.

The long-term results have been studied in 186 patients of the experimental group and 72 patients who had standard surgery. There was a reduction to 2.1 per cent of unsatisfactory results in the experimental group of patients in comparison with 5.8 per cent in controls.

Predictive factors of bile duct stones in patients undergoing cholecystectomy

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Bile duct stones are commonly identified by cholangiography. However, operative cholangiography increases the difficulty and duration of laparoscopic cholecystectomy, which is now the method of choice for management of gallstones. Intravenous cholangiography has a mortality rate of 0.8 per cent, and for endoscopic retrograde cholangiopancreatography (ERCP) the morbidity rate is 1 per cent and mortality rate 0.1 per cent. Therefore, it is important to perform these explorations only in patients in whom bile duct stones are suspected.

This study was undertaken to assess the value of preoperative clinical, biochemical and ultrasonographic examination in identifying duct stones, and to compare them with operative cholangiography.

From October 1990 to December 1991, 102 patients with symptomatic gallstones underwent open cholecystectomy. In all patients clinical examination including previous history of jaundice or pancreatitis, liver biochemistry and biliary tract ultrasonographic examination was performed before operation. All patients underwent operative cholangiography.

Thirty-three patients were found to have duct stones by operative cholangiography. The remaining 69 patients had a normal common bile duct. Nine factors were significantly more frequent in patients with duct stones: history of jaundice, elevation of serum level of total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and amylase, bile duct dilatation or evidence of duct stone by ultrasonography. These nine items were considered as risk factors for bile duct stone.

All patients with bile duct stone had at least one of these factors. Two had only one factor (history of jaundice and increase of serum direct bilirubin level), three had three factors, and 28 had four factors or more. When at least one factor was present, its sensitivity in prediction of bile duct stone was 100 per cent, its specificity 45 per cent, its positive predictive value 45 per cent and its negative predictive value 100 per cent.

So, in all patients presenting with at least one risk factor of bile duct stone, preoperative or operative cholangiography must be performed. In patients without any risk factor, there is no necessity for cholangiography.

Preoperative ultrasonography and liver function tests to identify patients for selective cholangiography

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Cholecystectomy without operative cholangiography reduces operating time and avoids unplanned common bile duct (CBD) exploration. To identify risk factors for CBD stones, records of 200 consecutive patients undergoing open cholecystectomy were reviewed. Any history of jaundice, pancreatitis or cholecystitis was recorded, as were preoperative bilirubin, alkaline phosphatase and alanine aminotransferase levels, and CBD size as measured on ultrasonography. These were correlated with operative findings and postoperative outcome.

Operative cholangiography was used in 177 cases, giving true negative results in 155, true positive results in 17 and false positive results in five. At operation, 26 patients had CBD stones (group I) and 174 did not (group II). Twenty-five group I patients had either a CBD diameter of >7 mm or at least one abnormal liver function test (LFT) (sensitivity 96 per cent). Of group II patients, 96 had both a non-dilated CBD on ultrasonography and normal LFT (specificity 55 per cent). If operative cholangiography had been restricted to patients with a dilated CBD or abnormal LFT, only one case of choledocholithiasis would have been missed, while 96 unnecessary operative cholangiograms and five unnecessary CBD explorations would have been avoided. We plan to use these investigations to identify future patients for selective cholangiography in association with laparoscopic cholecystectomy.

Prediction of low risk of common bile duct stones in gallbladder lithiasis

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In patients who have undergone laparoscopic cholecystectomy, intraoperative cholangiography is time-consuming and often unhelpful. The prediction of a low risk of common bile duct (CBD) stones should avoid the necessity of routine cholangiography.

Operative cholangiography was performed in 511 patients undergoing open cholecystectomy. Two subgroups were identified: patients with CBD stones visualized before CBD exploration ($n = 90$) and patients with no CBD stones on cholangiography ($n = 421$).

Multivariate analysis (stepwise logistic regression) showed that five variables were correlated with the presence of CBD stones: (1) size of CBD ≥ 12 mm; (2) gallstones ≤ 10 mm; (3) advanced age; (4) chronic or acute cholecystitis; and (5) history of biliary colic. The group of patients with a low risk (below 2 per cent) of CBD stones could be easily determined using a scoring system. In this group of patients operative cholangiography may thus be avoided.

Comparison of two different systems for predicting the need of peroperative cholangiography: contraindications of intraoperative cholangiography

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The aim of this study was to validate a predictive system for the detection of common bile duct (CBD) stones in patients undergoing cholecystectomy to establish a policy of selective peroperative cholangiography (POC).

A prospective analysis was performed of 230 consecutive patients undergoing cholecystectomy and routine POC to compare the predictive capability of the system when compared with POC findings. Patients included were all those who had submitted for elective cholecystectomy and recent ultrasonographic and biological studies.

The results for diagnostic properties, associated rate of retained stones and unnecessary POC performed are shown in the Table.

	SCORE	SWRS	Ultrasonography
Sensitivity	70.5	74.5	53
Specificity	80	72.5	95
Residual stones	7.0	6.1	13.2
Unnecessary POC	15.3	20.9	3.8

Values are percentages. SWRS, predictive equation derived from multivariate analysis of all factors; SCORE, system being validated

Our system is an easy way of predicting the presence of CBD stones. The equation derived from multivariate analysis increases diagnostic properties, although it requires computer processing. Ultrasonography is a non-reliable method of detecting CBD stones. Residual stones (undetected stones) were silent stones, i.e. unexpected POC findings; a value of 7 per cent compares favourably with data previously published with a 12 per cent incidence of unsuspected stones¹.

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Analysis of risk factors in cholecystectomy with common bile duct exploration

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A major goal in surgical research is to decrease mortality and morbidity rates after surgery. This can be achieved by the development of new techniques such as laparoscopic surgery, and also by thorough analysis of risks in standard operations.

The aim of this study was to find an objective indication for cholecystectomy with common bile duct exploration in cholecystocholedocholithiasis using methods of medical decision making.

Perioperative data were collected in a retrospective cohort study of 284 patients who underwent cholecystectomy and common bile duct exploration. Forty-nine parameters were analysed with respect to complications. In our patients death and gallstone left *in situ* rarely occurred, so that analysis of these did not seem sensible.

The total morbidity rate was 8.6 per cent and the mortality rate was 3.8 per cent. Analysis of single parameters revealed only emergency operations and congestive heart failure as individual risk factors in bile duct surgery. With the use of sophisticated mathematical calculations certain risk factor combinations can be identified and quantified. For instance, a patient with high creatinine and a high haematocrit had a 68 per cent chance of developing complications after surgery.

It is concluded that methods of decision making are useful even retrospectively in order to choose the best procedure in bile duct surgery. Analysis of risk factors can help to predict postoperative complications and may help in the selection of the optimal treatment for bile duct pathology.

Less invasive treatment of biliary stones or cholecystitis by combined medical and surgical approaches

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From March 1990 to October 1991, 233 consecutive patients were referred for laparoscopic cholecystectomy. In 26 per cent (60 patients) the indication was acute or delayed acute cholecystitis, six patients had biliary pancreatitis and four had cirrhosis. In ten patients the laparoscopic procedure was limited to biopsies (two malignancies) or was converted to laparotomy because of adhesions (four), cholecystenteric fistula (three) or cirrhosis (one). Mean (range) age was 58 (27–89) years; 15 per cent were over 75 years old. Preoperative assessment of the bile duct was by intravenous cholangiography in 6 per cent (14 patients) and by endoscopic retrograde cholangiopancreatography (ERCP) in 82 per cent (182 of 223 patients); bile duct stones were detected in 23 patients; they were treated with endoscopic sphincterotomy (ES) and stone extraction (incomplete in nine cases). Intraoperative cholangiography, performed in 88 per cent (197 of 223 patients), showed bile duct stones in 12 additional patients. In eight of these the preoperative ERCP was interpreted as normal, the other four did not have a preoperative ERCP. With intraoperative manipulations (flushing into the duodenum, crushing by ultrasonic contact lithotripter or transcystic extraction) these stones could be evacuated in 29 patients. Immediate postoperative ES and stone extraction was necessary in six patients (two with extracorporeal shockwave lithotripsy). Mean postoperative hospital stay was 3.2 days. Complications (thromboembolism and pulmonary infection) occurred in 6 per cent (14 patients); one patient needed postoperative ES with stenting for hepatic duct obstruction by a clip. There were no deaths.

In conclusion, preoperative and/or intraoperative cholangiography (not performed in 2 per cent of patients) revealed bile duct stones in 15 per cent of patients. Total cure of the biliary problem was achieved in all cases.

Biliary lithiasis in patients with cirrhosis

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The aim of this study was to evaluate the results of surgical therapy in patients with cholelithiasis and liver cirrhosis. Of 53 patients with

cirrhosis with biliary lithiasis, 31 were operated on. There were no emergency operations performed. Surgical procedures included cholecystectomy alone in 26, and cholecystectomy with common bile duct exploration in five patients. Patients in whom cholecystectomy was performed during operations for portal hypertension or other abdominal pathology were excluded from the study. According to the Child–Pugh classification, 28 patients were grade A, two were grade B and one was grade C. Symptoms consisted of typical biliary pain in nearly one-half of the patients and dyspepsia with abdominal pain in the others. Acute cholecystitis or cholangitis was present in five cases (16 per cent). Eleven patients had jaundice; the hyperbilirubinaemia was due to concomitant haemolytic disorders in two, common bile duct stones in five and mild liver failure in four.

There was no operative mortality. Postoperative complications included bleeding (eight cases), ascites (three cases), wound infection (two) and pulmonary (three) and metabolic (three) disorders. Bleeding was often associated with increased prothrombin time, more than 1.5 times above control, but severe haemorrhage occurred only when the platelet count was $<100\,000\text{ ml}^{-1}$. Two of the three grade B and C patients developed ascites.

In conclusion, biliary lithiasis occurs frequently in patients with liver cirrhosis. Cholecystectomy should be performed only in symptomatic patients with good hepatic functional reserve. Preoperative jaundice must be carefully investigated to avoid unnecessary common bile duct exploration.

Postcholecystectomy syndrome: the role of physiological disturbances after gallbladder removal

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There is an increased incidence of gastro-oesophageal reflux (GOR) in patients who have undergone cholecystectomy¹. A study was undertaken to determine prospectively whether cholecystectomy results in increased reflux and whether this is influenced by the type of operation.

Patients were studied before and 3 months after cholecystectomy by upper gastrointestinal endoscopy, gastric and oesophageal pH monitoring, and oesophageal manometry. Group 1 ($n = 30$) and group 2 ($n = 10$) underwent open and laparoscopic cholecystectomy, respectively.

	Open cholecystectomy	Laparoscopic cholecystectomy
Acid reflux score (DeMeester)		
Preop.	16.9(2.8)	16.1(5.0)
Postop.	33.7(7.0)*	34.4(5.8)*
Supine gastric pH >4 (percentage of time)		
Preop.	7.7(2.8)	14.5(4.0)
Postop.	13.7(5.9)	17.1(5.0)
LOSP (mmHg)		
Preop.	16.2(0.9)	13.8(0.1)
Postop.	15.3(1.2)	8.8(1.3)

Values are mean(s.e.m.). * $P < 0.05$ (Wilcoxon signed rank test)

Cholecystectomy resulted in increased GOR regardless of operative technique. Lower oesophageal sphincter pressure (LOSP) did not change significantly but there was a trend towards increased gastric alkalization which did not reach significance. Neural and hormonal mechanisms may link these findings, which have implications for patients with cholelithiasis and GOR.

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Fifteen years of experience with choledochoscopy in bile duct surgery

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Routine intraoperative choledochoscopy in the management of choledocholithiasis considerably improves the results and enables accurate diagnosis of bile duct neoplasms, cholangitis, cysts and iatrogenic damage to the bile ducts.

A total of 1010 intraoperative examinations was performed in 710 women and 300 men over a 15-year period. Intraoperative choledochoscopy showed bile duct disease in 205 (20 per cent) of patients. The mean age of the patients was 56.2 years. The most frequent indications were suspicion of choledocholithiasis or the assessment of the radicality of the operative procedure. The technique was also used to assess the degree of cholangitis and stenosis.

Over 60 per cent of examinations revealed cholangitis – almost half of these patients having reached an acute or advanced stage.

The diagnostic accuracy of choledochoscopy was subsequently compared with that of other bile duct examinations, such as endoscopic retrograde cholangiopancreatography and intraoperative cholangiography. There were no complications following operative choledochoscopy.

Laparoscopic cholecystectomy: current UK practice and attitudes to training

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The rapid adoption of laparoscopic cholecystectomy by the surgical community has raised questions about training for, and current practice in, this new technique. Guidelines have been issued by the Surgical Colleges. This study aimed to establish the extent to which these guidelines were being followed and to define current training and practice in the UK.

A questionnaire was posted to 1012 consultant general surgeons in the UK in July 1991. To date, 773 consultants (76.4 per cent) have replied of whom 680 regularly perform cholecystectomy. A total of 361 surgeons were already performing laparoscopic cholecystectomy while 210 of the remainder were planning to introduce it. Most of the 86 who had no such plans felt that they were too old or subspecialized, with only five surgeons (0.6 per cent) unconvinced of the benefits of laparoscopic cholecystectomy. Of those who were already performing laparoscopic cholecystectomy 68 (18.8 per cent) were self-trained but only nine (1.2 per cent) thought that training was unnecessary. Less than 20 per cent of those performing or intending to practice laparoscopic cholecystectomy felt they would have benefited from more training before introducing the technique. Of those who replied 231 (63.9 per cent) had performed fewer than 20 cholecystectomies with a median number of 10 (range 1–260). Of those performing laparoscopic cholecystectomy 161 (44.6 per cent) had previously practised diagnostic laparoscopy.

We conclude that the vast majority of UK surgeons are convinced of the benefits of laparoscopic cholecystectomy and appreciate the need for formal training. However, most consider themselves adequately trained although they have a limited practical experience of the technique.

Laparoscopic management of cholecystitis

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Laparoscopic cholecystectomy is currently considered the treatment of choice for uncomplicated, symptomatic cholelithiasis. Some 10–20 per cent of patients requiring cholecystectomy have cholecystitis. Cholecystitis has been considered as a contraindication to laparoscopic surgery because of the increased risk of complications. After a learning period consisting of 30 uncomplicated laparoscopic cholecystectomies, this procedure was attempted in patients with cholecystitis.

A total of 350 laparoscopic cholecystectomies was performed between March 1990 and October 1991; 56 patients (16 per cent) presented with acute or chronic (one or more episodes of acute cholecystitis during the past 6 months) cholecystitis. In four patients

(7.5 per cent) the procedure was converted to an open cholecystectomy (*versus* 1.7 per cent in the overall series). No morbidity was experienced in the 294 operations for uncomplicated lithiasis, while the morbidity rate in cholecystitis was three of 56 (5 per cent). A postoperative biliary abscess required laparoscopic management; bile leakage in a second patient resolved spontaneously; in the third case a common bile duct injury was detected during operation by cholangiogram and treated with a choledochojejunal anastomosis. Cholecystitis represents the main risk factor in this series of laparoscopic cholecystectomies (0 *versus* 5 per cent) with a morbidity rate comparable to that reported for open cholecystectomy (4–6 per cent)¹.

We conclude that in the presence of cholecystitis, laparoscopic management does not increase the risk of cholecystectomy provided there is routine use of intraoperative cholangiography and of subhepatic drainage; if any intraoperative difficulty or complication occurs, conversion to laparotomy should be undertaken.

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Laparoscopic treatment of acute cholecystitis

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Initial reports on laparoscopic cholecystectomy excluded patients with acute cholecystitis.

Between January 1988 and June 1991, 70 patients suffering from acute cholecystitis were surveyed. Open cholecystectomy was performed in eight patients, two of whom had undergone previous treatment with percutaneous cholecystostomy guided by ultrasonography. Laparoscopic cholecystostomy was performed on 62 patients, seven of whom had previously undergone percutaneous cholecystostomy treatment.

The results of the studies suggest that laparoscopic cholecystectomy may be performed, even in cases of acute cholecystitis.

In conjunction with percutaneous techniques, it may prove possible to treat acute cholecystitis with minimally invasive surgery.

Factors influencing the operative time for laparoscopic cholecystectomy

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In 1 year, 130 laparoscopic cholecystectomies were performed. The mean (range) operative time was 68 (30–260) min; it was <1 h in 68 cases (52.3 per cent) and >2 h in 28 (21.5 per cent).

Operations lasting >2 h were the first laparoscopic operation by each of the six surgeons on the service, or the first attempts at opacifying the biliary ducts (12 cases); in four cases there was difficulty related to the biliary tract (anomalies, aberrant duct, identification of the cystic duct) that required surgical caution; in five cases, chronic cholecystitis with sclerotic changes was present, and seven patients had acute cholecystitis (two empyema of the gallbladder). Five of these underwent emergency surgery; three were converted to open cholecystectomy (two for bleeding and one for slippage of a cystic duct clip).

Three principal factors influence the duration of laparoscopic surgery: the learning curve, the presence of acute or severe chronic lesions, and biliary anomalies. With experience, the effects of these factors (except the last) will be reduced, as was shown by the significant reduction in operative time in our practice (87 min for the first 60 cases, 51 min for the next 70 cases). This trend has not influenced the quality of the results.

Routine feasibility of laparoscopic treatment of acute cholecystitis or common bile duct stones

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From December 1989 to November 1991, a trial was undertaken to treat exclusively by laparoscopy complications of gallstones in 76 patients. Mean age was 61 (range 26–86) years. Eighteen patients were at high operative risk (American Society of Anesthesiologists

(ASA) grade 3, 14; ASA grade 4, four) essentially because of cardiovascular or pulmonary disease.

Sixty-six patients had macroscopic evidence of acute cholecystitis (39 catarrhal, 22 empyema, five gangrenous of whom one had generalized biliary peritonitis). In five cases (8 per cent) it was necessary to convert into a subcostal laparotomy because of bleeding or difficulty in the identification of anatomy. The mean length of operation was 152 (range 75–390) min.

Ten patients had common bile duct (CBD) stones. In nine cases, biliary decompression was completed laparoscopically (six by a transcystic procedure, three by choledochotomy). In one patient, a laparotomy was necessary. The mean length of operation was 195 min.

There were no deaths and the operative morbidity rate was 9 per cent (seven of 76 patients). Complications were five small parietal abscesses, one haemorrhage of the gallbladder bed, spontaneously resolved, and one pulmonary complication. Half of the patients left the hospital before the fourth postoperative day.

In conclusion, laparoscopic cholecystectomy for acute cholecystitis and laparoscopic treatment of CBD stones has a high level of feasibility (92 per cent) and a low incidence of complications considering the advanced age and concomitant diseases of some patients. Other studies are necessary to determine the exact role of laparoscopy in the management of CBD stones.

Role of routine preoperative intravenous cholangiography before laparoscopic cholecystectomy

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Many surgeons perform intravenous cholangiography (IVC) before laparoscopic cholecystectomy (LC) to detect choledocholithiasis and to gather information about the biliary tract anatomy. At the time of traditional laparotomy, IVC was shown to be of no value before cholecystectomy¹. The purpose of this study was to evaluate IVC before LC performed for symptomatic cholelithiasis, without acute cholecystitis, and with no evidence to suggest choledocholithiasis.

Of 230 consecutive patients with LC, the IVC of 153 patients with symptomatic cholelithiasis without cholecystitis or clinical and laboratory signs suggesting possible bile duct stones was reviewed. Two (1.3 per cent) of these patients had an allergic reaction to iodine, one of which was serious. Twelve (7.8 per cent) examinations were either unreadable or of poor quality, 139 cholangiograms were deemed normal and two showed stones. No anatomical variations were found, except seven cases where the cystic duct seemed to be short (< 15 mm).

During laparoscopy, intraoperative cholangiography was not routinely performed, but was carried out in ten cases. The two bile duct stones were confirmed by intraoperative cholangiography. Two additional bile duct stones were discovered after laparoscopy, even though the IVC had been interpreted as normal (sensitivity 50 per cent). The cystic duct was deemed as short when its length was <15 mm. Only two short cystic ducts were found among the seven, and two additional ones were found from among the 'normal' IVCs.

These results confirm that IVC is of poor sensitivity in detecting choledocholithiasis and presents a risk of hypersensitivity reactions. The routine use of IVC seems pointless before LC for symptomatic cholelithiasis without acute cholecystitis or in the absence of clinical suspicion of choledocholithiasis. Clinical and laboratory signs suggesting the presence of bile duct stones indicate the need to perform other investigations.

1. Houdart R *et al. Gastroenterol Clin Biol* 1990; **14**: 652–4.

Routine cholangiography is unnecessary for laparoscopic cholecystectomy

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Laparoscopic cholecystectomy is a minimally invasive technique for removing the gallbladder which has several theoretical advantages over traditional open cholecystectomy. The incidence of common bile duct (CBD) stones is approximately 15 per cent. Controversy

exists, however, as to whether selective or routine preoperative cholangiography should be performed during cholecystectomy. Over a 20-month period, 300 consecutive laparoscopic cholecystectomies without routine cholangiography were attempted. The conversion rate was 9 per cent.

	Cholangiography		ERCP		Total
	None	Perop.	Preop.	Postop.	
No.	229	5	27	11	272
Positive	0	0	7 (26)	2 (18)	9 (3)
Duct injury	2	0	0	0	2 (1)

Values in parentheses are percentages. ERCP, endoscopic retrograde cholangiopancreatography

The two duct injuries were identified and dealt with by open operation. These data indicate that only two of 240 patients (1 per cent) who did not have a preoperative or perioperative cholangiogram subsequently had symptomatic CBD stones. Thus, most CBD stones remain asymptomatic. Perioperative cholangiography may be indicated in selected patients who have had CBD symptoms or in patients in whom the biliary anatomy is unclear. However, routine preoperative or perioperative cholangiography is unnecessary for laparoscopic cholecystectomy.

Safety of laparoscopic cholecystectomy performed without operative cholangiography

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Intravenous cholangiography is inadequate to allow preoperative selection of a group of patients in whom operative cholangiography could be avoided and laparoscopic cholecystectomy performed with a low risk of common bile duct (CBD) stone.

Huguier and Lacaine, in a recent retrospective study, proposed a predictive computed score selecting two groups of patients at low risk (2 per cent) and high risk (46 per cent) of CBD stone. This score uses only five objective variables that are easily collected by clinical examination and preoperative ultrasonography. These factors are independent in multivariate analysis.

The five variables and their scores are:

- A. Age
- B. CBD diameter >12 mm (no = 0, yes = 1)
- C. Gallstone diameter <10 mm (no = 0, yes = 1)
- D. Biliary colic (no = 0, yes = 1)
- E. Cholecystitis (no = 0, yes = 1)

The overall score is calculated using:

$$\text{score} = 0.04 \times A + 3.1 \times B + 1.2 \times C + D + 0.7 \times E$$

A score <3.5 is defined as low-risk; score >3.5 as high-risk.

From February to December 1990, we prospectively studied 175 patients who then underwent conventional cholecystectomy with operative cholangiography. We used Huguier and Lacaine's scoring system and compared the results with operative cholangiography results. We were able to select a group at low risk of having a CBD stone (3.4 per cent if score <3.5) and a high-risk group (25 per cent if score >3.5).

It appears possible to perform laparoscopic cholecystectomy without any other investigation in the low-risk group. In the high-risk group, the performance value of other investigations, such as endoscopic cholangiography or endoscopic ultrasonography, and the real possibilities of laparoscopic operative cholangiography should be studied.

New strategy for common bile duct stones: combined endoscopic and laparoscopic treatment

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Common bile duct (CBD) stones are currently treated with open surgery, reserving endoscopic sphincterotomy (ES) for particular

cases; laparoscopic surgery might modify this option, being a less invasive treatment.

The first 300 cases of laparoscopic cholecystectomy (LC), operated on between March 1990 and November 1991 in this centre, were evaluated prospectively. Twenty-seven patients presented before operation with clinical, biological or ultrasonographic signs of CBD stones and were submitted to preoperative endoscopic retrograde cholangiopancreatography (ERCP) with ES. This demonstrated 19 cases of stones, six cases of recent migration ('traumatic papilla') and two false-positive cases: no complication occurred. These patients were submitted 24–72 h later to LC, with intraoperative cholangiography: two retained stones were found, and these were pushed into the duodenum by a transcystic Fogarty catheter; no conversion or complication occurred in this group. Mean hospital stay was 6.5 days. The 273 patients with no preoperative suspicion of CBD stones were directly submitted to LC; in 42 cases (15.4 per cent) with small stones and dilated cystic duct an intraoperative cholangiogram was performed: four cases (10 per cent) of CBD stones were found, and the treatment consisted of two transcystic extractions, one postoperative ES and one conversion to laparotomy. Among the 231 patients who did not undergo intraoperative cholangiogram, one returned 2 months later with a diagnosis of a residual CBD stone which was removed by ES. Global conversion rate was 5 per cent for elective LC and 26 per cent for urgent LC for acute cholecystitis; three postoperative complications were noted, one of which required laparotomy. Combined sequential treatment of CBD stones by a minimally invasive treatment appears to be an effective method of management with short hospital stay and a low complication rate. Acceptance of this method must consider the combined immediate and late (papillary stenosis) complication and failure rates of both ES and LC.

Human pericardium for reconstruction of benign iatrogenic common bile duct strictures in the pig

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Extrahepatic benign biliary tract strictures are usually iatrogenic. Despite technical advances in management, late strictures still occur. In an attempt to avoid bilioenteric anastomosis, various biological and artificial materials have been employed both clinically and experimentally, but no satisfactory replacement material has yet been found. The purpose of this study was to determine whether human pericardium could be used as a substitute for common bile duct (CBD) in experimental bile duct repair.

A midline laparotomy was performed in eight pigs weighing 20–25 kg under general anaesthesia and a subtotal stenosis produced over a 1-mm thick needle. Preoperative and postoperative parameters of cholestasis were measured weekly and CBD diameters measured by ultrasonography. After 3 weeks the CBD obstruction was replaced by a human pericardial patch using 7/0 Prolene (Ethicon, UK) single sutures without endoluminal stenting. After a further 6 weeks the CBD was dissected and a duodenotomy performed with intraoperative retrograde cholangiography. Finally the CBD was excised for histological examination and electron microscopy.

Mean (s.d.) preoperative CBD diameter was 4.5(0.54) mm; 3 weeks after the first operation it was 14.0(3.59) mm; 6 weeks after the second operation the value was 9.0(1.63) mm. Preoperative bilirubin levels were 0.375(0.09) mg dl⁻¹; 3 weeks after the first operation the value was 0.5(0.27) mg dl⁻¹; 6 weeks after the second operation the value was 0.325(0.05) mg dl⁻¹. Bilirubin could therefore not be used as a reliable indication for biliary obstruction.

In all cases the pericardial patch was overgrown by immature biliary epithelium, and no fistula or stenosis was observed within the 6-weeks observation period.

In this experimental model of bile duct stricture, bile duct injuries were repaired using human pericardium as a free graft. This proved to be an acceptable material for reconstruction of benign CBD strictures in the pig.

Treatment of benign biliary stricture: surgery versus endoscopy

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Benign biliary strictures (BBS) remain a therapeutic challenge. This study compared the results of surgery and endoscopy in one institution.

Between 1981 and 1990, 35 patients were treated surgically (ST) and 66 by endoscopic biliary stenting (ET). In almost all patients the initial trauma occurred during biliary tract surgery. Patient characteristics, previous repairs and levels of obstruction were similar in the two groups. ST consisted of constructing a biliary–digestive anastomosis in normal ductal tissue. ET consisted of placement of an endoprosthesis, with elective exchange every 3 months for a 1-year period.

In 35 ST patients a proximal hepaticojejunostomy was performed. Postoperative complications included: septicæmia (five), bile leakage (two) and major bleeding necessitating relaparotomy (two). ET-related early complications comprised: minor papillary bleeding (one), cholangitis (two) and pancreatitis (two). During treatment all complications were stent related: cholangitis (14), recurrent cholestasis (two) and stent migration (two). In 46 patients the endoprostheses were eventually removed.

After a mean follow-up of 50 (range 10–85) months, five of 35 ST patients (14 per cent) suffered re-stricture. Recurrent stricturing occurred in eight of 46 ET patients (17 per cent) after a mean period of follow-up of 42 (range 4–99) months. Subsequently, six patients underwent a hepaticojejunostomy and two were restented.

Surgical or endoscopic treatment of BBS yield similar results. Indications for ST are complete transections, previous repairs and failures of ET. Candidates for ET are those unfit for surgery or presenting with concomitant biliary fistula. In all other patients we advocate ET as the initial treatment.

Laparoscopic cholecystectomy and selective intraoperative cholangiography: a prospective series of 70 patients

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The aim of this study was to validate in a programme of laparoscopic cholecystectomy a scoring system which predicts the need for performing peroperative cholangiography (POC) to exclude common bile duct (CBD) stones.

This was a prospective study, in a series of 70 consecutive patients undergoing laparoscopic cholecystectomy, of a scoring system in which a cut-off value of five points indicates the need to perform POC. This system was previously studied in a series of 150 consecutive patients undergoing open cholecystectomy and compared with cholangiographic findings with the following results: 74 per cent sensitivity, 92 per cent specificity, a 4.6 per cent associated rate of undetected stones and a 6 per cent rate of unnecessary POC performed.

Patients with non-complicated gallbladder disease excluding obstructive jaundice were studied. Follow-up by clinical interview in all patients showed only two patients with clinical symptoms related to residual stones. One patient presented with obstructive jaundice and the other developed biliary colic without jaundice. This indicates an associated rate of residual stones of 3 per cent which compares favourably with the expected rate of the preliminary evaluation of the scoring system, indicating the possibility of spontaneous passage of stones through the papilla.

We conclude that patients undergoing laparoscopic cholecystectomy should undergo selective POC. Our system allows a policy of selective cholangiography by identifying patients at risk for CBD stones. The associated rate of undetected stones is lower than that expected from previous studies with routine POC, almost 12 per cent of unexpected findings in POC¹.

1. Schulemberg CAR. Operative cholangiography: 1000 cases. *Surgery* 1969; **65**: 723–30.

Congenital cystic dilatation of the common bile duct: late results of surgical treatment

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Cystic dilatation of the common bile duct (CBD) is a rare disease entity in Europe, but a well documented abnormality. Thirteen patients have been treated between 1980 and 1991 at the Charité Hospital. Eight were type I (cystic dilatation of the CBD), one was type II (diverticulum of the CBD) and three were type III (choledochoceles) of the classification by Todani. One patient developed a carcinoma in a choledochal cyst 23 years after a choledochocystojejunostomy. We treated this patient by a complete resection of the hepatic duct and CBD with the choledochocystojejunostomy. A Roux-en-Y hepaticojejunostomy was used to reconstruct the biliary tree. At follow-up at 35 months, the patient was doing well. The procedure of choice in the treatment of type I and II dilatations is primary excision of the CBD followed by a bilioenteric anastomosis if technically feasible. We were able to perform this in eight of our patients (seven type I and type II, and one type III). Only one patient suffered relapsing cholangitis attacks after this operative procedure, which were treated conservatively. The late mortality rate was 26 per cent. Two patients with a small choledochocoele have been treated by endoscopic papillotomy after which they were free of symptoms. Our experience confirms the need at any age for complete early excision of a choledochal cyst to prevent complications such as cholangitis, lithiasis and malignant change. Early excision of the choledochal duct should also be recommended in patients with choledochal cyst remaining after enteric drainage.

Endoscopic cystic duct occlusion and chemical gallbladder ablation

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Endoscopic gallbladder stone removal with a suction endoscope under epidural or local analgesia has previously been described¹. Combining this procedure with cystic duct occlusion and chemical ablation of the gallbladder mucosa would be an attractive alternative to cholecystectomy in elderly and high-risk patients. We investigated the feasibility of 'chemical cholecystectomy' in ten New Zealand White rabbits and eight Yukatan mini pigs. The rabbit cystic duct was surgically ligated and a mucosal exfoliant solution containing dithiothreitol (Stern's solution) was instilled into the gallbladder for 3 min. This was aspirated and replaced by 95 per cent ethanol and then by 0.3 per cent sodium tetradecyl sulphate. Rabbits were killed at 8 weeks. On histology nine of the ten rabbit gallbladders showed complete mucosal obliteration. This combination of chemicals was then used on the mini pigs. Endoscopic cystic duct diathermy was followed by catheter drainage with serial contrast radiography to determine occlusion by fibrosis. Cystic duct occlusion occurred in seven of eight pigs at 10 days. One pig required radiathermy to the cystic duct through the catheter tract. This duct was occluded after a further 8 days. Chemicals were then instilled into the gallbladder via the catheter. Pigs were killed at 12 weeks. On histological examination all pig gallbladders showed complete mucosal ablation and fibrosis without evidence of regeneration. Chemical *in situ* gallbladder ablation is safe and effective in animal studies.

1. Majeed AW, Reed MWR, Watkin DFL, Smart JG, Johnson AG. Sheffield cholecystoscope: new instrument for minimally invasive gallbladder surgery. *Br J Surg* 1991; **78**: 557-8

Endoprosthesis-related bile duct pathology: an experimental study in the dog

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The histopathological changes of extrahepatic bile ducts after a period of endoprosthesis biliary drainage (ED), and their consequences

for subsequent biliary tract surgery, were assessed in 21 mongrel dogs. Five dogs (group A) underwent ED for 4 weeks and were killed 2 months after removal of the stent. In six dogs (group B) 4 weeks of ED were followed by hepaticojejunostomy (HJ) and 2 months' observation. In five dogs (group C) the common bile duct (CBD) was ligated (4 days) and treated subsequently with ED (4 weeks) and HJ (2 months). In group D ($n = 5$) the effect of CBD ligation (4 days) and direct HJ (2 months) was studied. Stenting was accomplished by duodenotomy and CBD biopsies were obtained during HJ and at autopsy. Bile samples were cultured during each step of the procedure.

Endoprosthesis biliary drainage of both a normal and obstructed CBD resulted in a distended fibrosing bile duct, showing severe chronic inflammation with epithelial hyperplasia of the mucosa. At 2 months after removal of the stent the inflammation was still moderately present. A higher incidence of postoperative (infectious) complications was noted after biliary tract surgery with previous endoscopic stenting.

Group	CBD inflammation		Positive bile culture (%)		Postop. complications	
	Pre-ED	Post-ED	4 weeks	2 months	Infectious	Non-infectious
A	-	+++	100	80	1	0
B	-	+++	100	100	3	1
C	+	+++	100	100	2	1
D	-	+	30	100	0	1

Biliary lithiasis in elderly patients: results with open surgery

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A retrospective study was performed over the period from 1982 to 1991. Over this time, 90 patients of mean age 84.7 (range 80-95) years underwent operation for biliary stones. The study comprised 18 men and 72 women. Forty-eight per cent came from home and 57 per cent came from a nursing home for old people. Seventy-three per cent were admitted as emergencies. General health was good in 33 per cent, moderate in 46 per cent and poor in 21 per cent. More than 90 per cent of the patients presented with one or more associated pathologies. Cholecystectomy was performed in every case. The management of ductal stones has been analysed for two time periods: 1982-1987 (group 1) and 1987-1991 (group 2).

Group 1: of 52 patients treated, 17 had ductal stones. Sixteen patients had a choledochoduodenotomy performed. Only one patient had an endoscopic sphincterotomy performed before operation.

Group 2: of 38 patients treated, 12 had ductal stones. Eleven patients had an endoscopic sphincterotomy (two preoperative, nine postoperative).

The postoperative period was uncomplicated in 69 per cent of patients. The operative mortality rate was 10 per cent (12 per cent group 1, 7.5 per cent group 2). All deaths were after emergency surgery (three had had anastomoses). Risk of death was not related to age.

In conclusion, these elderly patients should have elective surgery rather than more risky emergency treatment. Results are improved by the addition of endoscopic techniques.

Laparoscopic techniques have not been applied specifically to elderly patients. However, the need for emergency treatment in patients with other pathologies may limit the scope of laparoscopic surgery. It is also important to remember the excellent results of the conventional surgical approach.

Raised plasma cholecystokinin after cholecystectomy or truncal vagotomy and pyloroplasty

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Cholecystectomy or truncal vagotomy and pyloroplasty (VP) may alter the mechanisms that control postprandial release of cholecystokinin (CCK).

Plasma CCK concentrations were measured using a CCK-specific radioimmunoassay before and for 60 min after a standard meal of 60-ml corn oil in instant mashed potato in 13 adult controls, nine patients after VP, in 22 patients before cholecystectomy for symptomatic uncomplicated gallstones, and in 20 patients after cholecystectomy.

	Control	VP	Before cholecystectomy	After cholecystectomy
Fasting CCK (pm)	0.6(0.1)	0.7(0.06)	0.9(0.15)	0.7(0.07)
Peak CCK (pm)	3.0(0.5)	11.3(1.9)*	4.9(0.9)†	5.2(0.7)
Integrated CCK (pmol l ⁻¹ h ⁻¹)	123(18.7)	409(68.7)*	188(29)†	229(28.9)

Values are mean(s.e.m.). **P* < 0.001; †*P* < 0.03 versus control (Mann-Whitney *U* test)

Plasma CCK concentration is significantly increased after VP. Circulating levels of CCK after VP may be sufficient to contribute to postvagotomy symptoms and could be regarded as pathological.

Plasma CCK is significantly raised after cholecystectomy. This may be a feature of the gallstone disease rather than cholecystectomy as CCK is also elevated in patients with gallstones before cholecystectomy. The small but significant increase after cholecystectomy demonstrates a physiological effect which may not have pathological significance.

In vitro study of cinnarizine and cimetidine in the human gallbladder

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An *in vitro* study of human gallbladder strips was carried out with isometric tension in an organ bath. Disease-free gallbladders from patients of either sex and variable age were used. For each strip, dose-response curves were plotted to assay the effects of histamine alone (2×10^{-9} to 2×10^{-4} M), followed by curves to study the effects of H₁ and H₂ antagonists (cinnarizine and cimetidine respectively, at increasing doses: 10^{-6} , 10^{-5} , 10^{-4} M). Each antagonist was added 30 min before plotting dose-response curves for histamine. Maximum effect (*E*_{max}) (mg mm⁻²), median effective dose (ED₅₀) or pD₂ was determined for both cinnarizine and cimetidine.

Responses were compared by ANOVA and the Newman-Keuls test for multiple comparisons between all treated and control groups corresponding to each drug employed.

Cinnarizine and cimetidine did not affect basal tone of the gallbladder strips; cinnarizine induced dose-dependent decreases in contraction, its antagonistic effect being characterized by a curve displacement towards higher concentrations of agonist, with a decrease in *E*_{max}. Cimetidine in turn displaced the dose-response curve towards a lower concentration.

Our results indicate that antagonists bind to H receptors but also leave the latter partly accessible, for contraction continued after incubation with the antagonist; alternatively, histamine partly displaces the antagonists, as a maximum effect was not achieved. Cinnarizine reduces, while cimetidine increases, the contractile response of the human gallbladder smooth muscle on utilizing histamine as agonist.

	<i>E</i> _{max}		
	Mean(s.e.m.)	<i>F</i>	<i>P</i>
Control	207.0(24.3)	1.583	0.210
Cinnarizine (10^{-6} M)	193.7(8.9)		
Cinnarizine (10^{-5} M)	182.0(19.8)		
Cinnarizine (10^{-4} M)	153.9(27.6)	4.538	0.008
Control	196.79(24.1)		
Cimetidine (10^{-6} M)	206.4(6.5)		
Cimetidine (10^{-5} M)	238.7(18.0)		
Cimetidine (10^{-4} M)	259.9(9.5)		

	pD ₂		
	Mean(s.e.m.)	<i>F</i>	<i>P</i>
Control	5.8(0.2)	12.859	0.000
Cinnarizine (10^{-6} M)	5.4(0.2)		
Cinnarizine (10^{-5} M)	4.8(0.4)*		
Cinnarizine (10^{-4} M)	4.6(0.3)*	3.775	0.018
Control	5.6(0.2)		
Cimetidine (10^{-6} M)	5.5(0.3)		
Cimetidine (10^{-5} M)	5.7(0.4)		
Cimetidine (10^{-4} M)	6.5(0.2)*		

Values are mean(s.e.m.) of *E*_{max} and pD₂. Six strips were used in each case. *Differs significantly from control response

Effects of H₁ and H₂ antihistamines and anticholinergic agents on guinea-pig gallbladder muscularis

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A study is made of the actions of H₁ antihistamines (cinnarizine, flunarizine), H₂ antagonists (cimetidine, famotidine) and anticholinergic hyoscine bromide on guinea-pig gallbladder muscularis, evaluating the degree to which the cell membrane contributes to the effects of these antagonists. Guinea-pigs of either sex (600–750 g) were used. Gallbladder segments were prepared and stripped of their serosa. An organ bath and isometric transducer was used to record changes in tension. Maximal tension was dispelled by repeatedly washing with Ca²⁺-free relaxing solution, allowing tension to dissipate for 20 min before plotting additional dose-response curves. At the end of each assay we made a challenge with 100 mM

	<i>E</i> _{max}		
	Mean(s.e.m.)	<i>F</i>	<i>P</i>
Control	124.1 (6.4)	7.753	0.003
Cinnarizine (10^{-5} M)	86.5 (8.5)		
Cinnarizine (10^{-4} M)	58.3 (4.7)		
Control	123.5 (4.9)	20.676	0.001
Flunarizine (10^{-5} M)	91.0 (8.1)		
Flunarizine (10^{-4} M)	60.6 (8.1)		
Control	130.5 (11.3)	0.451	n.s.
Cimetidine (10^{-5} M)	125.4 (10.3)		
Cimetidine (10^{-4} M)	138.8 (10.1)		
Control	129.7 (5.9)	0.088	n.s.
Famotidine (10^{-6} M)	129.9 (8.6)		
Famotidine (10^{-5} M)	133.2 (5.8)		
Control	122.4 (8.2)	0.053	n.s.
Hyoscine bromide	120.7 (11.6)		
Hyoscine bromide	125.9 (11.0)		

Values are mean(s.e.m.) of *E*_{max} (mg-F); six strips were used in each case. n.s., Not significant

Biliary

acetylcholine. Maximum effect (E_{max}) was calculated and an ANOVA and Newman-Keuls test were used for multiple comparisons. Gallbladder strips built tension in response to low doses of Ca^{2+} . The log concentration-effect curves for Ca^{2+} resulting from these experiments all had steep slopes; maximal response was seen with 20 mM. The 100 mM acetylcholine challenge at the end of each experiment caused no increase in tension. The results obtained for the different drugs employed are shown in the Table.

Cinnarizine and flunarizine were found to antagonize the contractile effects induced by Ca^{2+} . This was attributed to their ability to act on different cell components, i.e. on the cell membrane and intracellular contractile elements. In contrast, hyoscine bromide, famotidine and cimetidine appear to act only on the cell membrane of the guinea-pig gallbladder smooth muscle.

Palliative treatment of multiple biliary papillomatosis facilitated by percutaneous use of the flexible choledochoscope

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Multiple biliary papillomatosis is exceedingly rare and involvement of the pancreatic duct has been described in only a few cases in the world literature. The disease is characterized by multiple attacks of cholangitis or pancreatitis due to obstruction of the ducts by the papillomas or the secreted mucus, leading ultimately to death from sepsis or liver failure, usually within 2 years of diagnosis. Treatment must be directed towards extensive excision if long-term survival is to be expected. Palliative measures consist of repeated drainage and curetting of the bile ducts by surgical or endoscopic means.

An 80-year-old man with massive involvement of both hepatic and common bile ducts as well as the pancreatic duct underwent a hepaticoduodenostomy with internal stenting of both right and left hepatic ducts as a means of palliative internal drainage. However, because of recurrent obstruction and displacement of the drains, external drainage became necessary and was achieved by insertion of a percutaneous transhepatic stent in the right hepatic duct and through the hepaticoduodenostomy. Progressive dilatation of the stent tract allowed the introduction of the flexible choledochoscope, through which repeated aspirations and curetting were performed under direct vision, without imposing a great strain on the patient. The percutaneous use of the flexible choledochoscope proved to be a valuable tool in the palliative treatment of this rare disease and obviated the need for frequent surgical or endoscopic intervention.

Primary carcinoma of the gallbladder: a review of 143 cases

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The records of 143 patients with gallbladder carcinoma treated operatively between 1973 and 1990 were reviewed retrospectively. There were 115 women and 28 men, with an average age of 69.3 (range 36–89) years. Gallstones were present in 73.4 per cent of the patients. The symptoms of primary carcinoma of the gallbladder were similar to those of other forms of biliary tract disease. Abdominal pain was the most common symptom and was present in 103 of the 143 patients (72.0 per cent). Jaundice was present in 83 patients (58.0 per cent) and weight loss in 68 (47.5 per cent). A preoperative diagnosis was made in only 28.7 per cent of cases. The duration of symptoms varied between 3 days and 17 months. Surgical procedures included cholecystectomy alone (24 patients), cholecystectomy with biliary drainage (82 patients), cholecystectomy and resection of the hepatic bed (17 patients) and exploration with biopsy or bypass (20 patients). In 95.8 per cent of cases the histological type was adenocarcinoma. Only 21.5 per cent of the patients underwent curative surgery.

The overall 5-year survival rate was 11 per cent. For patients whose tumour was limited to the gallbladder wall (T_{1b} , T_1 , T_2), the actuarial 5-year survival rate was 41.5 per cent. For patients with T_3 and T_4 tumours, the 5-year survival rate was nil.

The prognosis depended mainly on the depth of tumour invasion. For the early stages, the survival rate may be higher with a more aggressive surgical procedure. For the usually observed tumours which extend beyond the gallbladder, the prognosis has not been improved.

Proximal extrahepatic bile duct tumours: experience with 23 cases

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Twenty-three patients with proximal extrahepatic bile duct tumours (EBDT) were treated at our institution between 1975 and 1990. There were 17 men (74 per cent) and six women (26 per cent). The mean age was 62 (range 35–86) years.

At presentation, all patients were jaundiced and three had cholangitis. Diagnosis was established by ultrasonography, endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography, and computed tomography. Localization of the tumour at the bile duct bifurcation was: type I 21.7 per cent, type II 43.5 per cent and type III 34.8 per cent (Bismuth–Corlette classification). Complete resection of all macroscopic tumour was accomplished in eight patients (group 1). The final histology report revealed microscopic evidence of tumour at the proximal resection margin in six of these eight patients. In the remaining 15 patients the cancers were advanced, with involvement of surrounding structures or distant metastases. These patients underwent palliative procedures: group 2 patients underwent palliative resection (five patients), and in group 3 (ten patients) intrahepatic cholangiojejunostomy was performed in three patients and transtumoural intubation was carried out in seven patients. The 30-day hospital mortality rate was none in group 1, 40 per cent in group 2, and 40 per cent in group 3. The morbidity rate was 25 per cent in group 1, 80 per cent in group 2 and 60 per cent in group 3. Mean survival time was longer in group 1 compared with the two other groups (30.4 versus 6 months).

Long-term survival in patients with EBDT is rarely achieved even in those cases (35–50 per cent) in which complete resection of the tumour can be performed. Local recurrence is the usual cause of death, the tumour spreads along the periductal vessels and may infiltrate the intrahepatic ducts over a wide distance, the retro-duodenal tissues of the hilar area and the hepatoduodenal ligament. EBDT should be considered as regional rather than local disease. Total hepatectomy with complete resection of the biliary system and its lymphatic drainage tract by means of a Whipple procedure followed by liver transplantation offers a more radical approach and might produce better survival rate or even definitive cure in a selected group of patients.

Early versus delayed cholecystectomy in acute cholecystitis

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The exact incidence of acute cholecystitis in patients with gallstones is not known, but approximately 20 per cent of patients who enter a hospital for biliary tract disease have acute cholecystitis (2.5–3 per cent of the total admissions to a general surgical unit). The appropriate timing of operation is still debated.

This study presents 143 cases of acute cholecystitis studied during a period of 3 years. They were divided into group 1: patients operated on within 72 h of hospital admission; group 2: patients operated on more than 72 h after hospital admission.

	Group 1 (n = 67)	Group 2 (n = 76)
No. of patients		
M	36 (54)	26 (34)
F	31 (46)	50 (66)
Age (years)	67.9	72.6
Medical condition, diabetes, renal failure	29 (43)	38 (50)
Surgical complications	11 (16)	12 (16)
Biliary complications	3 (4)	7 (9)
Medical complications	6 (9)	39 (51)
Mortality		
Biliary	0	1
Medical	2 (3)	6 (8)
Length of stay (days)	12.4	20.8

Values in parentheses are percentages

Treatment was decided on the basis of the clinical status and medical condition. The treatment in both groups was cholecystectomy. All cases received antibiotic prophylaxis.

Sex, age, medical conditions, past history, surgical complications, biliary complications, medical complications, mortality rate, length of stay, and total cost for each group was recorded. The results are shown in the *Table*.

The group operated on within 72 h had fewer surgical, biliary, or medical complications and lower mortality rate. All these factors lead to an increase in hospital stay and hospital costs. For this reason early cholecystectomy should be performed in all cases. Medical conditions must be corrected as soon as possible.

Choice of laparotomy or laparoscopy for acute cholecystitis

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Two techniques for the surgical management of acute cholecystitis are compared: nine of 18 patients were treated by laparotomy—five primarily (three cases of empyema of the gallbladder in old and fragile patients, two because of lack of experience or equipment) and four by conversion after failure of a laparoscopic approach due to haemorrhage (two cases), biliary leakage (slippage of a clip from a retracted cystic duct stump), or to massive empyema secondary to adenocarcinoma of the gallbladder.

Nine other patients were treated by laparoscopy: six cases of acute cholecystitis and three patients with empyema of the gallbladder. All were punctured under endoscopic control before ablation (bacteriology showed three patients were infected with *Escherichia coli*, four with *Streptococcus D*, one with *Proteus* sp.). In eight cases the operative site was drained by closed suction drains. The mean duration of surgery was 110 (range 85–250) min. All patients received piperacillin during and for 2–5 days after surgery.

There was no mortality. The mean ages of the two groups were similar (67.0 versus 67.1 years). Normal diet was resumed earlier in the group undergoing laparoscopy (28 versus 70 h), morbidity was lower (one lymphangitis versus three, two wound infections and one respiratory problem) and the hospital stay was shorter (5.2 (range 3–7) days versus 10.5 (range 5–23) days) than in the group undergoing laparotomy.

Despite a high rate of conversion (four of 13; 31 per cent), which should decrease with experience, it is legitimate to propose a laparoscopic approach in acute cholecystitis. It is wise to abandon this technique if precluded by either local or general conditions.

New approach to the treatment of patients with acute cholecystitis, suppurative cholangitis and biliary abscesses of the liver

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A new method of delivery of antibiotic to the liver and biliary system by autologous erythrocyte ghosts has been developed experimentally and applied clinically in 120 patients with acute cholecystitis, five patients with biliary abscesses of the liver and in five with suppurative cholangitis. We infused intravenous ghosts containing a single dose of antibiotic only twice a day.

Pharmacokinetic investigation has shown a higher concentration (3–4.7 times) of antibiotic in the bile of patients receiving antibiotic by the new method compared with patients who received intravenously, intramuscularly and even endolymphatic infusion of antibiotic. In patients who received antibiotics by the new method the amelioration of immunological, biochemical and clinical features was more marked.

The patients with biliary abscesses of the liver and suppurative cholangitis were treated without operation.

No septic complications of disease or urgent operation was noted in patients with acute cholecystitis who were at high risk of requiring urgent operation. They underwent an elective operation after detailed examination and preoperative management of multiple system disorders. The mean(s.d.) disappearance of clinical and laboratory symptoms of disease was 1.9(0.01) days compared with 9.0(0.4) days for patients who received traditional conservative therapy.

On the basis of this analysis we can say that this new method is effective, economical and can be used in biliary surgery.

Acalculous chronic biliary disease: criteria for operation

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Acalculous biliary disease is poorly understood. Fifteen years of experience on 350 patients undergoing operation in this clinic confirmed the need for thorough investigations to avoid excessive cholecystectomy. In such situations we consider it necessary to specify some criteria for surgical intervention: prolonged clinical biliary discomfort that does not improve over 4–6 months of adequate treatment; biliary secretion rate measured by duodenal aspirate accompanied by the presence of cholesterol crystals in bile sediment; morphological and functional modifications noted at standard cholecystcholangiographies accompanied by the persistence of gallbladder opacification for 36 h and especially for 60 h; echographic detection of gallbladder wall thickening as a consequence of cholesterol deposits; exclusion of other diseases which may produce similar symptoms; existence of pancreatic, sphincter of Oddi or duodenal disorders secondary to biliary disorders or the possible persistence of radiologically and echographically invisible microcalculi.

Compliance with these principles has led to the disappearance of the so-called 'postcholecystectomy syndrome'.

Choledochoduodenostomy versus hepaticojejunostomy in choledocholithiasis: a randomized controlled trial

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In choledocholithiasis, when biliary–enteric anastomosis is indicated, the surgeon may choose between choledochoduodenostomy (CD), which carries a risk of cholangitis by duodenal content reflux through the common bile duct, and hepaticojejunostomy (HJ), which is more time consuming and which precludes further endoscopic exploration. As yet, one technique has not been shown to be superior to the other in controlled trials.

Between January 1978 and November 1990, 130 patients (31 men and 99 women), mean(s.d.) age 61(15) years, entered this randomized study. A CD was performed in 64 patients, while an HJ was performed in 66 (side-to-side in 25 cases and end-to-side in 41). The major endpoint was the occurrence of cholangitis within 3 years following the operation, defined as biochemical cholestasis with or without fever or pain. Other criteria were postoperative mortality, morbidity, and reoperations on the main bile duct.

Postoperative mortality rate was 3.8 per cent (five patients); there was no statistical difference between the two groups (four in the CD group and one in the HJ group). Postoperative morbidity was not different: one biliary fistula occurred in the CD group (2 per cent) and five in the HJ group (8 per cent).

Late results in 120 patients (mean(s.d.) follow-up 55(11) months) showed that 107 patients (89.2 per cent) had no symptoms related to biliary–enteric anastomosis. Cholangitis episodes occurred in 13 patients (10.8 per cent) (six in the CD group and seven in the HJ group, with no statistical difference). Cholangitis occurred during the first year in eight patients (62 per cent) and during the second year in five patients (39 per cent). No case of ulcer was found in the HJ group.

This randomized controlled trial confirms the good results of both CD and HJ in choledocholithiasis, with similar mortality and morbidity rates, and 90 per cent asymptomatic patients in long-term follow-up. Nevertheless, these results favour the use of CD in choledocholithiasis, because CD is easier and quicker to perform than HJ, and does not preclude further endoscopic exploration.

Choledochoduodenostomy versus sphincterotomy in the treatment of choledocholithiasis: assessment of 351 patients

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The aims of this study were: (1) to review the present indications for supraduodenal choledochoduodenostomy (CDD) and transduodenal sphincteroplasty (TSP) in our unit; (2) to analyse the frequency of

postoperative complications and to estimate the perioperative mortality rate; and (3) to study the long-term clinical outcome of both operations.

Over a 10-year period 2610 patients underwent operation for biliary lithiasis. Exploratory choledochotomy was indicated in 591 (22.6 per cent). This was followed by simple choledochorrhaphy over a T tube in 240 cases (40.6 per cent), TSP and choledochorrhaphy over a T tube in 126 (21.4 per cent), CDD in 216 (36.5 per cent) and CDD plus TSP in nine (1.5 per cent).

CDD was performed if the bile duct was >12 mm in diameter. The indication for TSP was the presence of a stone impacted in the papilla and/or papillary stenosis.

The rate of intra-abdominal complications in the early postoperative period was 4 per cent for CDD (six cases of intra-abdominal abscess and three of external biliary fistulae) and 3.7 per cent for TSP (four cases of abscess and one of acute pancreatitis). The mortality rate for patients with CDD was 1.8 per cent (three cases of pulmonary complications and one of biliary fistula) and for patients with TSP was 0.7 per cent (one case of pulmonary complication).

After a mean follow-up period of 5.6 years, 71.5 per cent of patients undergoing CDD and 76 per cent of patients undergoing TSP were asymptomatic. The remainder suffered from dyspepsia, colicky pain or episodes of cholangitis. Ten patients (six CDD and four TSP) underwent reoperations for residual calculi.

In conclusion, we stress the low operative morbidity and mortality rates of both CDD and TSP operations and the excellent long-term results.

Endotoxin levels following treatment of obstructive jaundice

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In a controlled study, the influence of taurolidine on the endotoxin level in the blood was tested in 25 patients. All the patients were hospitalized with obstructive jaundice. Using a standardized procedure, taurolidine 20 g day⁻¹ was infused by a central venous line over 4 days as a perioperative and postoperative treatment. Before and after operation, endotoxin levels were measured and analysed with the *Limulus* assay. None of the patients initially received antibiotic therapy.

Five patients were operated on for cure (three Whipple procedures, two liver resections). Eleven underwent a bypass procedure. The remaining nine patients were treated with an endoscopically or radiologically inserted stent.

Twenty-two of these patients showed a very low endotoxin level that lay within the normal range. Five patients developed sepsis but only two demonstrated high endotoxin levels. Two of the 25 patients died following surgical intervention.

In conclusion, taurolidine is a very promising agent to control the endotoxin level in high-risk patients.

Postoperative bile leakage: endoscopic management

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Postoperative bile leakage is a serious complication, in which surgical treatment has its limitations. This study evaluates endoscopic management.

Between 1982 and 1990, 55 patients (28 female, 27 male; mean age 55 years) were referred with postoperative bile leakage. Initial surgery was cholecystectomy in most cases. T tubes were employed in 17 patients. The patients presented with a biliary-cutaneous fistula (27), peritonitis (ten), recurrent intra-abdominal abscess formation (five), progressive jaundice (seven), cholangitis (five) or pancreatitis (one). The mean interval between initial surgery and presentation was 37 (range 5–292) days. Therapy consisted of standard sphincterotomy with subsequent stone extraction when appropriate, with or without endoprosthesis placement. The aim of treatment in all cases was to facilitate bile flow into the duodenum.

The biliary tract and the site of the leakage were visualized during endoscopic retrograde cholangiopancreatography in 98 per cent of cases. The site of leakage was the cystic duct stump (37), the common hepatic duct (six), the common bile duct (six), a hepatic radicle (four) and a surgical anastomosis (one). Distal obstruction due to retained

gallstones was present in 15 patients and to concomitant strictures in 18. Overall, 48 of 55 patients were treated endoscopically: sphincterotomy (11), sphincterotomy and stone extraction (ten), stone extraction and stent placement (five), stent placement (19) and stent placement followed by nasobiliary drainage (three). An excellent outcome (clinical and radiological improvement and closure of the bile fistula) was achieved in 43 patients (90 per cent). Despite adequate therapy, five patients (10 per cent) had ongoing sepsis resulting in a fatal outcome.

Postoperative bile leakage can be diagnosed effectively by endoscopic retrograde cholangiopancreatography and treated safely by subsequent endoscopic management in 90 per cent of patients, but the mortality rate of such management remains significant.

Laparoscopic cholecystectomy: initial experience

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A total of 41 laparoscopic cholecystectomies have been performed since June 1990 on 39 women and two men with a mean age of 38.5 (range 23–67) years. The indication for this procedure was symptomatic cholelithiasis; 29 cases presented with biliary colic, 11 cases with chronic cholecystitis and one case with acute cholecystitis. The diagnosis was confirmed by ultrasonography. Operation time ranged from 65 to 245 (mean 95) min. There were no bleeding or bile duct injuries. No patient required conversion of the laparoscopic procedure to an open cholecystectomy. Mean hospitalization time was 3.5 days. There was no mortality. The morbidity was 7.3 per cent (umbilicus wound infection was noted in three cases). The median time to full activity after discharge was 15.5 days.

It is concluded that laparoscopic cholecystectomy offers an alternative method of treatment for cholelithiasis.

Diffuse-form Caroli's disease: a surgical dilemma

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Caroli's disease is a rare condition with an incidence of one per million, and is characterized by congenital dilatation of the intrahepatic bile ducts. The bile duct anomaly may in 20 per cent of cases be limited to a liver segment or lobe, but in its usual form it affects the entire intrahepatic biliary tree. In the latter form, biliary drainage techniques have often proved ineffective in preventing recurring bouts of cholangitis. Moreover, resection of the most severely affected liver parenchyma is seldom feasible because of associated congenital hepatic fibrosis or secondary biliary cirrhosis. In such cases, orthotopic liver transplantation (OLT) may represent the only treatment, but the optimal timing of this procedure has yet to be determined. In these typically young and otherwise healthy individuals, OLT may be perceived by the patient and practitioner as an unacceptable burden. Later, however, if acute cholangitis resistant to antibiotics develops, the patient may no longer be suitable for OLT.

The case of a 31-year-old man is reported, in whom the diagnosis of diffuse-form Caroli's disease associated with congenital hepatic fibrosis was made at the age of 12 years, when the patient developed his first attack of acute pancreatitis due to migration of an intrahepatic bile duct calculus. After endoscopic sphincterotomy, the patient remained asymptomatic for 5 years. In August 1990, he developed acute cholangitis with ensuing septic shock and acute respiratory distress syndrome. At laparotomy, all superficial liver cysts were fenestrated in order to remove intrahepatic bile stones. Bile duct anomalies in the left liver lobe were minimal, but the idea of performing a right hepatectomy was abandoned because of the small size of the left lobe and the existence of associated congenital hepatic fibrosis. Resection would almost certainly have led to acute hepatic failure and encephalopathy. The patient is alive and well 8 months after operation, but remains at risk of developing life-threatening cholangitis.

In diffuse-form Caroli's disease, biliary drainage, whether surgical, endoscopic or percutaneous, is ineffective in preventing recurring cholangitis, and is associated with a poor long-term prognosis. Furthermore, these patients have a 10 per cent risk of developing bile duct carcinoma, an incidence 100 times that in the normal population. In these patients OLT may be the only effective treatment.

Mirizzi's syndrome: scintigraphic diagnosis

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In some patients, obstruction of the cystic duct by a stone is associated with partial obstruction of the common bile duct. This is Mirizzi's syndrome. In this condition, fistulation of the cystic duct into the common bile duct may occur, either spontaneously or after surgery. It is therefore important to make this diagnosis before operation, a difficult matter since the clinical and biochemical parameters are similar in patients with acute cholecystitis, with or without Mirizzi's syndrome. In the past year, however, ultrasonography, computed tomography, scintigraphy and endoscopic retrograde cholangiopancreatography have shown their value in the diagnosis of this condition.

In this paper we analyse the clinical and biochemical features of 24 patients affected by Mirizzi's syndrome (from 250 patients

undergoing operation for acute cholecystitis), and also the diagnostic value of HIDA-DISIDA scintigraphy in this condition. Over the past 10 years, we have also analysed 200 patients with acute cholecystitis who had preoperative biliary scintigraphy. In 24 cases, Mirizzi's syndrome was detected (18 women, six men) at the time of operation.

Neither clinical features (pain in the right upper quadrant, vomiting or fever), nor biochemical parameters (leucocytosis, elevation of alkaline phosphatase, bilirubin or γ -glutamyl transpeptidase) differed in patients with or without Mirizzi's syndrome. In contrast, scintigraphy offered a highly sensitive and specific pattern, consisting of: (1) non-visualization of the gallbladder; (2) moderate dilatation of the main hepatic bile duct; and (3) delayed excretion into the duodenum. Therefore, in our experience the prevalence of Mirizzi's syndrome among patients with acute cholecystitis is 8.8 per cent, and ^{99m}Tc -HIDA-DISIDA scintigraphy is a highly sensitive and specific method of diagnosing Mirizzi's syndrome.

Cytology and prognosis in breast cancer

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Moriquand *et al.* have suggested that some cytological criteria are correlated with prognosis in patients with breast cancer. This report is a study of smears from fine needle aspiration biopsies in relation to the clinical progress of 74 patients submitted to mastectomy for breast cancer between 1 January 1983 and 31 December 1985. The following have been considered: tumour node metastasis classification, receptor status, follow-up and cytological grading based on a modification of Moriquand's criteria: some changes had to be made owing to our use of Papanicolaou instead of May-Grünwald-Giemsa staining. Cytological grading was based on the cellular (isolated or in cell clusters, cytoplasmic volume) and nuclear aspects (distribution of chromatin, anisokaryosis, naked or gemmant nuclei), presence and dimensions of nucleoli and number of mitoses. A grading from I to III was given, adding the scores assigned (from 1 to 3) to all the parameters considered. A score of <5 corresponded to a grade I (more favourable prognosis); a score of 5–9 corresponded to a grade II; a score of >10 corresponded to grade III (unfavourable prognosis).

In 74 positive cytological smears, 17 (23 per cent) were grade I, 48 (65 per cent) were grade II and 9 (12 per cent) were grade III. After 5 years, of the patients with grade I, eleven (65 per cent) are alive and without recurrence, four (24 per cent) are lost to follow-up, and two (12 per cent) are dead. Among those with grade II, 36 (75 per cent) are alive and well, six (12 per cent) are lost to follow-up, and six (12 per cent) are dead. Finally, of those with grade III, one (11 per cent) is alive and well, two (22 per cent) are lost to follow-up, and six (67 per cent) are dead.

We suggested this method because there is a good concordance between cytological grading and prognosis and it is simple and cheap.

Non-palpable breast lesions: indications for fine wire localization and biopsy

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The use of mammography has produced an increase in the number of non-palpable cancer breast lesions diagnosed. Preoperative localization of the suspicious area and hookwire-directed biopsy under local anaesthesia are necessary to discriminate between benign and malignant lesions.

From October 1988 to June 1991, 92 cases of non-palpable breast lesions detected by mammographic screening were seen (mean patient age 52.4 (range 33–69) years). Radiological findings and histological results were: 19 (21 per cent) well defined masses (one infiltrating ductal carcinoma and 18 benign lesions); 36 irregular masses (39 per cent) (seven infiltrating ductal carcinomas, one infiltrating lobular carcinoma, two *in situ* carcinomas, one mucinous carcinoma and 25 benign lesions); 23 (25 per cent) microcalcifications (one ductal *in situ* carcinoma, one lobular infiltrating carcinoma and 21 benign lesions); 13 irregular masses with microcalcifications (14 per cent) (five ductal infiltrating carcinomas, one ductal *in situ* carcinoma, one ductal, lobular, *in situ* and infiltrating carcinoma, one ductal and lobular *in situ* carcinoma, one lobular infiltrating carcinoma and four benign lesions); one (1 per cent) irregular mass with macrocalcifications (one ductal infiltrating carcinoma).

These data confirm the need to perform needle localization and biopsy of non-palpable breast lesions when irregular masses and/or clustered microcalcifications are present.

Microdochotomy in the treatment of juxta-areolar mastitis

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Much confusion still exists regarding the aetiology and treatment of juxta-areolar mastitis. Whereas it was earlier thought that obstruction

of lactiferous ducts resulting in their dilatation was the cause of the relapsing symptoms, recent reports suggest periductal inflammation as the primary cause.

Between January 1985 and December 1989, 20 women (median age 42 (range 24–66) years) were seen with this disease. Two patients had bilateral involvement. Breast pain in 11 (55 per cent) and nipple discharge in 16 (80 per cent) patients were the most common complaints. Nipple inversion was present in nine patients (45 per cent) and a palpable mass in only four. Median duration of symptoms was 24.4 (range 1–85) months. Almost one-half of the patients had been previously treated, usually by a combination of antibiotics and multiple drainage procedures. All of these patients had recurrence. Mammography was carried out in all cases but showed no peculiarities in nine (45 per cent), while benign inflammatory lesions were seen in the remainder. Ductography performed in seven women demonstrated dilated ducts in two and papillomas in three patients.

All women underwent microdochotomy (excision of the diseased duct and its drainage system) with partial excision of the nipple. The nipple was closed while the areolar skin was left open. Microscopic investigation of the specimen showed periductal inflammation and duct ectasias in 15 patients (75 per cent). The others showed no findings other than chronic inflammation. Follow-up ranged from 7 to 53 months. Two patients (10 per cent) showed postoperative problems: one had a recurrent nipple discharge; the other suffered from a relapsing abscess. All other patients were symptom free.

Microdochotomy with partial nipple excision appears to be the treatment of choice for this benign but troublesome condition, in which periductal inflammation seems to be responsible for the symptoms.

Evaluation of axillary lymph node involvement in operable breast cancer: comparison of clinical and histological findings

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The purpose of this study was to assess the efficacy of clinical examination in the preoperative detection of axillary lymph node involvement in operable breast cancer. The study group consisted of 162 women with breast cancer, treated in the period 1970–1989. All patients underwent radical surgery with axillary dissection.

At presentation, axillary lymph nodes were not clinically palpable in 68 patients (42.0 per cent) (N_0 according to the tumour nodes metastasis system). Palpable homolateral nodes were present in the remaining 94 women: N_1 in 90 patients (55.6 per cent) and N_2 in four cases (2.5 per cent). Postoperative pathological examination of the lymph nodes revealed axillary metastases in 70 patients (43.2 per cent).

In the T_1 group there was no histological node involvement, and all these cases were also clinically considered node negative. In the T_2 group positive axillary nodes were found in all cases with N_{1b} and N_2 , and the preoperative evaluation in these patients was fully adequate. However, nodes not palpable (N_0) or felt to contain no metastases (N_{1a}) were involved in 44.2 per cent of cases in this group. Among the T_3 cases, clinical evaluation of the axillary lymph nodes was less misleading. All patients who were considered to have lymph node involvement had positive nodes on pathological examination.

Comparison between these data shows that preoperative clinical evaluation of the axillary lymph nodes in women with operable breast cancer gives false-negative results in 38.5 per cent. There were no false-positive results in this series.

Immune responsiveness of peripheral lymphocytes at presentation with breast cancer: a series of 110 consecutive patients

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Breast cancer is a disease which appears to have a wide range of biological behaviour, with aggressive disease not always identified at presentation using routine clinical methods. The aim of this study was to evaluate the cell-mediated immune response of breast cancer

patients at presentation in order to identify potential aggressive disease.

A total of 110 consecutive patients presenting with breast cancer over a 3-year period was evaluated. Controls were 34 normal women. Peripheral blood was drawn and separated using standard Ficoll techniques. Peripheral lymphocytes were subsequently tested for responses to the mitogens phytohaemagglutinin (PHA), concanavalin A (Con A), and the production of interleukin 2 (IL-2).

Mean(s.e.m.) lymphocyte blastogenesis in response to PHA in controls was found to be 54 905(2790). Significant PHA suppression was shown in 24 patients: 19 772(1557), $P < 0.0001$. The remainder showed no suppression (51 008(1990)). The situation was similar with responses to Con A: controls 53 619(3335) versus suppressed 20 137(1028) ($P < 0.0001$). IL-2 production in patients suppressed to both PHA and Con A was significantly suppressed compared with controls: 55.4(21.4) pg per 0.1 ml versus 7.28(2.08) pg per 0.1 ml, $P < 0.02$.

We conclude that there exists a subpopulation of breast cancer patients who are immunosuppressed at presentation with decreased production of IL-2. This may help identify aggressive disease in the future.

Routine radionuclide bone scanning and liver ultrasonography in patients with breast cancer

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A 3-year prospective study was performed on all patients presenting with *de novo* invasive breast carcinoma at two surgical units, to assess the benefit of routine perioperative radionuclide bone scanning and liver ultrasonography.

A total of 358 patients was analysed. Pathological staging by the tumour node metastasis (TNM) classification categorized 133 as stage I, 188 as stage II and 37 as stage III. Bone scans were performed on 339 patients (94.7 per cent), of whom 302 had stage I or II disease and 37 had stage III. Three patients (0.9 per cent) with stage I or II disease had metastases demonstrated, whereas six (16 per cent) stage III patients had positive scans.

None of 309 patients (96.3 per cent) with stage I or II disease had liver metastases demonstrated by ultrasonography. Two patients (5 per cent) with stage III disease had positive scans.

A total of 611 bone and liver scans was performed on the patients who were deemed to have stage I or II disease, at a cost of approximately £50 000. Three of these scans altered the patient's stage but none changed their management. Routine radionuclide bone scanning and liver ultrasonography can be abandoned in stage I and II breast cancer, thus allowing a considerable saving of resources without adversely affecting the patient's prognosis.

Anomalies in the region of the human progesterone receptor gene in primary breast cancer

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The aetiology of primary breast cancer is thought to involve a complex interplay of hormonal and genetic factors. To date, a number of specific mutations have been described with regard to the tumour DNA of breast tumours but little work has focused on the much more fundamental question of whether there exists an intrinsic genetic predisposition to the development of this disease. This is especially relevant in breast cancer given its recognized familial predisposition. Epidemiological data also imply a role for steroid hormones in its pathogenesis.

The human breast cancer cell line T47D was screened for human progesterone receptor (PR) complementary DNA (cDNA) and a 1.85-kb insert was isolated. This was confirmed as a clone for the PR cDNA by restriction analysis and Southern blotting and sequencing. DNA from a series of 47 breast tumours and 42 blood samples was isolated and probed following digestion with TaqI.

In eight of 42 blood samples and 11 of 47 tumours, a distinctive 1.9-kb fragment was obtained. None of 40 healthy controls displayed this fragment. Early clinical follow-up has shown no significant differences between those displaying this anomaly and those not.

This is the first description of the isolation and use of a probe for the PR gene and the first description of abnormalities in breast cancer patients in the region of this gene. Work continues to determine the exact nature of this anomaly.

Potentiation of the response to chemotherapy in patients with breast cancer by dietary supplementation with L-arginine

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A phase I study was performed to determine the response of locally advanced breast cancers to neoadjuvant chemotherapy and radiotherapy in patients supplemented with L-arginine. By increasing protein synthesis in human breast cancers, arginine may sensitize these cancers to cell cycle-specific chemotherapeutic agents.

To date, 23 patients (25 tumours) with breast cancer (T_2 , $n = 2$; T_3 , $n = 15$; T_4 , $n = 8$) have received oral arginine (30 g day^{-1}) for 3 days followed by CHOP (cyclophosphamide, 1 g m^{-2} ; Adriamycin, 50 mg m^{-2} ; vincristine, 1.5 mg m^{-2} and prednisolone, 40 mg) orally for 5 days. This cycle was repeated at 21-day intervals for four cycles. Subsequently, all patients received radiotherapy (50 Gy to the breast and 45 Gy to the lymph draining areas).

Following chemotherapy alone, 22 of 23 patients (24 of 25 tumours (96 per cent)) have had a clinical response: seven tumours (28 per cent) had a complete response (CR – no palpable tumour), and 17 tumours (68 per cent) showed a partial response (reduction >50 per cent of the product of two maximum perpendicular diameters). Subsequent radiotherapy resulted in a further reduction in tumour size but no increase in CR. The one patient who had not responded to chemotherapy and radiotherapy initially received an additional two cycles of CHOP-arginine (large T_4 tumour) and obtained a partial response. Imaging modalities (mammography and ultrasonography) revealed a response rate of 48 per cent (12 of 25) and 64 per cent (16 of 25) after chemotherapy and 75 per cent (12 of 16) and 80 per cent (12 of 15) after radiotherapy. Histological responses of biopsies/mastectomies are currently being evaluated.

In conclusion, in this study the response of breast cancer to chemotherapy is one of the highest ever documented. L-Arginine, therefore, is able to enhance the response of breast cancer to chemotherapy.

Internal mammary artery and superficial jugular vein as recipient vessels for free transverse rectus abdominis musculocutaneous flap breast reconstruction

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Breast reconstruction using the free microvascular transverse rectus abdominis musculocutaneous (TRAM) flap proves to have fewer vascular complications and donor site morbidity than the pedicled TRAM.

Most authors select the thoracodorsal vessels as recipient vessels. The disadvantages of these vessels are difficult access in the supine position, severing of the main blood supply of the latissimus dorsi, radiation damage after axillary radiotherapy, and lateral positioning of the most prominent part of the reconstructed breast, bringing zones III and IV to the medial aspect of the reconstructed breast.

To maintain an intact blood supply to the latissimus dorsi, and to improve the venous drainage of the entire very large, free TRAM flap, the following recipient vessels were selected: homolateral internal mammary artery at the sixth to seventh intercostal space and the external jugular vein, which is brought down from the mastoid through a simple neck skinfold incision, turning it down over the clavicle and through the pectoralis major muscle.

The advantages of this technique are a more medial positioning of the TRAM zones I and II, with improved breast projection, without ptosis, and enhanced arterial input, so that all four zones of the TRAM, including its skin, can be used in both obese and slim patients. It is our experience that radiotherapy to the internal mammary artery is less damaging than on the thoracodorsal or acromioclavicular vessels. Furthermore, there is improved venous drainage, thereby avoiding the most frequent TRAM problem. The veins of the internal mammary artery are usually too small to drain a huge TRAM flap.

Breast

In ten consecutive cases no marginal necrosis or wound problems were encountered, even in patients with very severe radionecrosis and ulceration.

Results of treatment of locally advanced breast cancer

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In 152 patients admitted in our clinic between 1984 and 1988 with locally advanced breast cancer, choice of therapy depended on tumour stage and local aspect. Treatment was locoregional therapy

(preoperative or postoperative radiation and surgical treatment) followed by systemic chemotherapy (30 patients) or neoadjuvant chemotherapy followed by surgery and/or radiotherapy (91 cases). The 31 patients who declined surgery were treated by chemotherapy and/or radiotherapy.

Surgery consisted of 29 cleaning mastectomies, ten Halsted and 82 Madden mastectomies completed by 35 oöphorectomies.

In 112 patients followed up, 88 per cent operated on and 24 per cent who declined surgery, the results were as follows: all of the non-operated patients died within 3 years; 58 of the operated patients were alive after 3 years, 40 after 5 years and 14 after 7 years.

In conclusion, surgery reasonably completed with preoperative or postoperative chemotherapy ensures a better survival rate, especially in IIb and IIIa stages.

Quality of life on circulatory support

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During recent years the number and success rate of staged cardiac transplantation has increased. In most series 70–75 per cent of supported patients come to transplantation, and their survival rate is equal to, and sometimes even better than, that of 'normal' heart transplant recipients. This analysis was carried out to evaluate the quality of life before cardiac transplantation while on circulatory support.

Between January 1986 and December 1990, 20 patients were supported using an implantable, pneumatic left ventricular assist device. In this group of patients, attention was directed towards changes in haemodynamics, end-organ perfusion, nutritional intake, mobility and improvement in New York Heart Association (NYHA) functional class while on support.

Five patients died while waiting to receive a donor heart and 15 patients were transplanted after a mean support time of 99 days. During the total time of the support, all survivors had normal renal and hepatic function. Most patients were fed orally. Of the 11 long-term survivors, nine were able to function in NYHA class I while assisted, which improved their pretransplant condition.

It is concluded that life on circulatory support while waiting for cardiac transplantation provides a near-normal existence for patients imminently facing death without this option.

First rib abnormalities in association with cervical ribs: a preventable cause of recurrent symptoms

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Operative intervention for symptoms of thoracic outlet syndrome (TOS) is associated with a failure to relieve symptoms or an early recurrence in up to 40 per cent of patients.

Of 56 patients undergoing surgery for TOS, 24 had cervical ribs, eight presenting with occlusion or aneurysm of the subclavian artery. A total of 30 cervical rib operations was undertaken including four for recurrent symptoms. Review of the angiograms indicated that the principal site of vascular compression in the patients with recurrent symptoms was at the level of the first thoracic rib. In addition, seven new patients presenting with cervical ribs have been prospectively studied and arterial obstruction has clearly been shown to occur at this level in all of these patients. Surgical treatment to include simultaneous resection of first thoracic and cervical ribs via an anterior approach was effective in all cases.

All resected specimens have been examined and these demonstrate variable gross first rib abnormalities which would not have been corrected by cervical rib excision alone. We consider that the presence of this anomaly in at least 20 per cent of patients with a cervical rib is a significant cause of postoperative morbidity which can be avoided by careful preoperative assessment and appropriate modification of surgical technique.

Diagnosis and management of 40 cases of aneurysm of the descending thoracic aorta

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During the 6-year period 1986–1991, 453 patients were treated surgically for aortic aneurysms of all types (ascending, descending or abdominal). Of these, 31 patients (25 men and six women, mean (range) age 62 (40–77) years) underwent operation for aneurysm of the descending thoracic aorta. Of these aneurysms, 16 were dissecting, 11 atherosclerotic and four post-traumatic. Most of the atherosclerotic aneurysms were asymptomatic, although a few patients developed hoarseness, haemoptysis, dysphagia or haematemeses. The dissecting aneurysms were associated mostly with

chest pain, pleural effusion or haemothorax when ruptured, and sometimes with ischaemia of the lower extremities.

For these 31 patients, emergency or elective surgery was performed as indicated. In a further nine patients conservative antihypertensive treatment alone was instituted. The main surgical procedures used were aortic replacement and unroofing and patching. The mean (range) occlusion time was 38 (18–56) min. No extracorporeal circulation was used.

Twenty-three patients survived the operation. Three died during surgery (ruptured aneurysm) and five within 30 days of operation. There were two cases of postoperative paraplegia. The first (occlusion time 18 min) recovered completely after 8 months and the second (occlusion time 52 min) is making a slow recovery.

In conclusion, descending thoracic aortic aneurysm is a serious disease with high morbidity and mortality rates. The shortest occlusion time is always desirable, although neither this nor any other measure prevents the development of paraplegia.

Experimental and first clinical experiences with implantable ultrasonographic Doppler probes used to evaluate postoperative bypass patency after coronary surgery

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In cases of early postoperative bypass occlusion quick intervention has been impossible because of a lack of diagnostic techniques. Furthermore, the basic pathophysiological mechanisms (bypass thrombosis, competitive blood flow) remain unclear. We present a new, miniaturized, temporarily implantable 20-MHz ultrasonographic probe which is fixed on to the bypass graft. This probe should help to determine postoperative bypass patency.

At first, this pin-head sized ultrasonographic Doppler probe was tested in human veins by means of a circulatory model with electromagnetically controlled flow. Subsequently, during coronary bypass surgery, these probes were implanted in ten patients and flow measurements were performed up to the third day after operation (five left anterior descending artery, three right circumflex artery, two right coronary artery). The ultrasonographic impulses were stored electromagnetically, digitized and analysed by Fourier transformation. A semiquantitative measurement of the bypass flow allowed estimation of the bypass quality.

By application of the Doppler equation a correlation between Doppler impulse and flow within the circulatory model can be clearly demonstrated. In ten patients the Doppler probes were used during operation. One early occlusion of a left anterior descending artery graft was diagnosed; in this case, thrombectomy was performed successfully.

During the postoperative phase, this miniaturized implantable ultrasonographic probe allows on-line performance of semiquantitative flow measurements of small vessels. With the help of the Fourier transformation an early bypass stenosis or bypass thrombosis might be detected from modification of the flow profile. This method also allows a semiquantitative evaluation of pharmaceutical approaches to modification of coronary blood flow during the early postoperative phase.

Isolated blood-perfused large-heart model for studying recovery after cold *ex vivo* storage

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It would be of value to establish a simple and reliable model for studying recovery after induced cold chemical cardioplegia (CCC) and *ex vivo* hypothermic storage imitating the situation prevailing in handling of the donor heart during cardiac transplantation. In this study, pig hearts of a size comparable to the human adult heart were subjected to different periods of global ischaemia, and reperfused with blood in an isolated Langendorff model.

The study consisted of three groups of hearts. Group I ($n = 11$) hearts excised from slaughterhouse pigs were subjected to 9 min of warm ischaemia before induction of 171 min CCC; group II ($n = 8$) hearts were excised from anaesthetized pigs and subjected to 180 min CCC; group III ($n = 8$) hearts were excised from anaesthetized pigs and subjected to 90 min CCC. Bretschneider's procaine-containing solution was used to induce CCC. After induction of CCC the hearts were stored in cold saline at 5°C until mounted in the reperfusion model, and then reperfused for 120 min.

Three hearts in group I were excluded from further analysis, one because of 'stone heart' phenomenon, and two owing to increasing left ventricular end diastolic pressure. No hearts in the two other groups were excluded. The functional, metabolic and ultrastructural recovery during the reperfusion period were the same in groups II and III, which is in accordance with data from the literature. However, the functional recovery in hearts from group I was significantly lower and the myocardial lactate and citrate release significantly higher during reperfusion than in hearts in groups II and III. Furthermore, at the end of the cardioplegic period the ultrastructure of the hearts in group I had deteriorated compared with the two other groups. These differences confirmed the increased ischaemic burden and damage of hearts in group I animals.

This model, which uses pig hearts comparable in size, anatomy and function to human hearts, is simple and reproducible, and seems suitable for evaluating recovery after ischaemia during *ex vivo* storage.

Heterozygosity for homocystinuria: an independent risk factor for vascular disease

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Homocystinuria is a prominent risk factor for premature atherosclerotic disease. To explore the frequency of homocystinuria in young patients aged <50 years with peripheral vascular disease, excessive methionine accumulation after a standardized methionine load was determined.

Patients were considered to be heterozygous for homocystinuria when peak levels of homocysteine after methionine loading exceeded the mean control levels by more than 2 s.d. There were no conditions known to disturb methionine metabolism, such as renal failure, liver cirrhosis, vitamin B₆ or folate deficiency.

In a pilot study ($n = 25$), heterozygosity for homocystinuria was found in nine (36 per cent) patients. The probability of identifying heterozygotes in the normal population has been estimated to be one in 70 at the most. Therefore the high frequency of heterozygotes in our group with premature occlusive peripheral disease is evidence of an increased risk of atherosclerosis.

Based on these results we started a prospective study of the prevalence of homocystinuria in young patients ($n = 360$) with symptoms of cardiac, cerebrovascular and/or peripheral atherosclerosis. Treatment with vitamin B₆ might prevent a number of serious clinical sequelae of homocystinuria. In all our patients a 6-week course of treatment resulted in normal homocystinuria values. In addition, a randomized intervention study with vitamin B₆ treatment was carried out and all patients monitored for new atherosclerotic events.

These data show that a substantial proportion of patients with early-onset vascular disease have impaired homocysteine metabolism. This impaired metabolism can be treated easily.

Model for acute haemodynamic studies downstream of vascular end-to-side anastomoses in pigs

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The study was conducted in order to evaluate an animal model for acute haemodynamic studies of vascular end-to-side anastomoses, with special reference to anastomotic geometry, angle of anastomosis and influence of different degrees of stenosis in the proximal outflow segment.

The abdominal aorta of pigs weighing 90 kg was dissected retroperitoneally and all branches between the superior mesenteric artery and the trifurcation other than the right renal artery were ligated. The proximal anastomosis was made distal to the superior mesenteric artery and the total bypass length held constant, while the angle of anastomosis was varied. The geometry of the anastomotic area, the degree of stenosis and the different angles of anastomosis were determined during the operation by angiography and by post-mortem casts.

For initial studies the Vingmed CFM 750 colour Doppler device was used. A special facility allowed downloading of velocity information from every pixel in the colour Doppler image to a Macintosh computer for further processing.

As the flow fields were reproducible and the regions with disturbed flow were in agreement with those of studies *in vitro* reported in the literature, the model was found valid for further investigations *in vivo*, including measurements of accurate velocity profiles and turbulence distribution as a function of the above-mentioned parameters.

Management and outcome of prosthetic valve endocarditis

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Prosthetic valve endocarditis (PVE) is an infrequent but serious complication of cardiac valve replacement. Between 1987 and 1990, 1066 patients underwent surgery for heart valve replacement in our hospital. During this time we treated 39 episodes of PVE in 35 patients. There were nine episodes of early (< 60 days) and 30 episodes of late PVE.

Symptoms, clinical signs and laboratory data were similar in both early and late PVE. Fever was the most consistent sign, occurring in 36 of 39 episodes (92 per cent), compared with an erythrocyte sedimentation rate of >50 in 27 (69 per cent), anaemia in 26 (67 per cent) and leucocytosis in 18 (46 per cent). The development of a new murmur in 23 of 39 patients (59 per cent) carried a poor prognosis if not surgically managed. Aortic root abscesses occurred in ten patients and were associated with atrioventricular conduction block in five. Blood cultures were positive in 32 of 39 episodes, with *Staphylococcus epidermidis* being cultured in all nine early and 12 of 30 late PVE. Vancomycin and rifampicin were used as initial treatment in all cases unless another pathogen was isolated. Initial management was surgical in 23 episodes and medical in 16. Of those medically managed, 11 were cured, three died and two re-presented within 1 year with PVE. In the surgically managed group, two required further repeat operations for control of sepsis and heart failure, both surviving. Follow-up of cases ranged from 1 to 46 months. The mortality rate of three of nine for early and seven of 30 for late PVE compares favourably with that of other series.

In our series *S. epidermidis* was the most common pathogen isolated and there were clear predictors of prognosis. Early aggressive antimicrobial therapy and surgical intervention will influence the outcome of PVE.

Skeletal muscle transformation for cardiac assist

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Transformation of skeletal muscles by chronic electrical stimulation has made dynamic cardiomyoplasty a reality. However, during preconditioning by electrical stimulation muscles undergo atrophy and lose power. This could be a limiting factor.

In this study we describe the effectiveness of 2 weeks of stretch, with or without electrical stimulation at 10 Hz, in preconditioning the latissimus dorsi muscle of rabbits. Stretch was maintained at approximately 110 per cent of the muscle's resting length. Latissimus dorsi muscles subjected to electrical stimulation alone underwent significant atrophy. In contrast, stretched and stimulated muscles increased their mass, both in length and cross-sectional area. The latter muscles could generate more absolute power than the former. When normalized for differences in cross-sectional area the power output (i.e. per kilogram) was reduced by 40–50 per cent in both cases. Electrical stimulation alone and stretch combined with

stimulation resulted in similar significant increases in fatigue resistance, relative to both control and stretched-only muscles.

The longer and more powerful muscles produced by combining stretch with electrical stimulation should facilitate the surgical wrapping of enlarged hearts and act as more forceful assist devices.

Influence of ventilatory changes on three-dimensional velocity profiles in the main porcine pulmonary artery system

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Knowledge of detailed haemodynamics in the pulmonary arteries is of importance in understanding cardiac and pulmonary diseases.

In order to investigate the haemodynamic aspects of single-lung atelectasis, ten 90-kg pigs underwent selective intubation by a double-lumen tube. The pulmonary trunk and its main branches were exposed after opening the chest. Central haemodynamic monitoring was used. Thermodilution and electromagnetic flow meters calibrated by Doppler ultrasonography were used in determining blood flow distribution.

Blood velocity was measured at 17 points evenly distributed over the cross-sectional area, using a C shaped perivascular five-element 10-MHz ultrasonographic Doppler transducer, which was rotated by increments of 45°. The transducer was mounted one diameter downstream to the pulmonary valves and over the pulmonary bifurcation. Measurements were performed under normal, right and left lung atelectasis.

Velocity profiles were plotted through the cardiac cycle. One diameter downstream to the pulmonary valves the profiles showed the highest velocities against the right superior vessel wall, with diastolic retrograde velocities inferiorly and superiorly. At the bifurcation two jets were shown corresponding to the two main branches and no retrograde velocities were seen. With single-lung

atelectasis the velocity profiles showed jets against the ventilated lung.

These findings expand previous data on our knowledge of haemodynamics in the pulmonary artery.

Impact of reduced myocardial function on the results of cardiac surgery

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Left ventricular function that is impaired before operation may influence the results of cardiac surgery. The purpose of this study was to look for standard haemodynamic measurements that can provide a reliable guide to the success of coronary artery surgery or valve replacement.

The influence of ejection fraction (EF), left ventricular end-diastolic pressure (LVEDP) and cardiac index (CI) on survival after coronary artery bypass grafting (CABG), aortic valve replacement (AVR) and mitral valve replacement (MVR) were analysed.

A total of 5200 patients who underwent operation from 1980 to 1990 was included in this retrospective study. In 4484 patients having CABG only, an EF ≤ 40 per cent was associated with increased early mortality (2.9 versus 1.2 per cent; $P < 0.05$) and late mortality (mean(s.d.)) 5-year survival rate, 79.8 (6.5 versus 89.5(1.5) per cent; $P < 0.05$). In 188 patients receiving AVR for aortic regurgitation none of the analysed parameters reached significance. In 349 patients having AVR for aortic stenosis only, a CI $< 2.01 \text{ min}^{-1} \text{ m}^{-2}$ was associated with increased early mortality (13.3 versus 2.5 per cent; $P < 0.05$). In 179 patients treated by MVR for mitral regurgitation only, an LVEDP $\geq 20 \text{ mmHg}$ was associated with increased early mortality (14.3 versus 3.9 per cent; $P < 0.05$).

The results show that the parameters reflecting impaired left ventricular function are dependent on the underlying disease. The data may be helpful in identifying patients at high risk of perioperative mortality and in improving the timing of surgical intervention.

Colon and rectum

Whole-gut irrigation in large bowel surgery

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The purpose of this study was to evaluate the effectiveness of whole-gut irrigation in the prophylaxis of septic complications after reconstructive large bowel surgery.

Before closure of a loop or lateral colostomy, two methods of bowel preparation were compared. The routine method (diet, purgatives and enemas) was used in 168 patients, while whole-gut irrigation was used in 48 patients. Irrigation was performed 20 h before operation using a solution with NaCl (7.0 g l^{-1}), KCl (0.75 g l^{-1}) and NaHCO_3 (3.0 g l^{-1}). Six to eight litres of solution were required. No oral antibiotics were administered in either group.

Postoperative complications occurred in 88 patients (52.4 per cent) after routine bowel preparation and in 16 (33 per cent) after whole-gut irrigation ($P < 0.05$). Wound infection occurred in 30 (17.9 per cent) and anastomotic leak in eight patients (4.8 per cent) after routine bowel preparation. No patient had a wound infection or anastomotic leak after whole-gut irrigation.

Whole-gut irrigation is the preferable method, diminishing the frequency of wound infection and anastomotic leakage.

Once- versus twice-daily dosing regimen of amikacin in prophylactic use in elective colorectal surgery

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A group of 118 patients undergoing elective colorectal surgery was included in a prospective study from May 1989 to December 1990. They were randomly assigned to receive either a single high dose of $15 \text{ mg kg}^{-1} \text{ day}^{-1}$ of amikacin (group 1) or a 7.5 mg kg^{-1} dose in a twice-daily regimen (group 2). Metronidazole was administered three times per day. In both groups prophylaxis was limited to 24 h.

Peak concentrations (30 min after 30 min infusion) and trough concentrations (24 h) were measured. Culture specimens were taken at the time of surgery. Renal and otovestibular function were assessed before and after surgery. Blood urea nitrogen and serum creatinine levels were recorded. Otovestibular toxicity was evaluated by interview, clinical examination, audiogram (0.25–8 kHz) and electronystagmogram.

Mean (s.d.) peak amikacin concentrations were $52.7(21.1) \text{ mg l}^{-1}$ in group 1 and $30.2(28.1) \text{ mg l}^{-1}$ in group 2. Trough concentrations were $1.1(1.2)$ and $2.8(1.3) \text{ mg l}^{-1}$ respectively. Both regimens provided peak serum levels above pathogen MIC values. Resistance of isolated pathogens to amikacin was not observed. Infective complications occurred in ten cases (17 per cent) of group 1 and 11 (19 per cent) of group 2. Six patients (10 per cent) and five patients (8 per cent) respectively presented surgically related septic complications. Both results were not significantly different (Student's *t* test). There was no detectable renal toxicity. Only one case of possible auditory alteration was recorded on audiogram (group 2).

Because of the therapeutic peak levels and the less toxic trough levels, neither efficacy nor safety seem to be compromised by a single high dose of amikacin. Since it offers an advantage of convenience a once-daily regimen of amikacin is preferable to a twice-daily schedule for prophylaxis in elective colorectal surgery.

Treatment of perforated diverticulitis

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An analysis of a national multicentre study of the latest trends in management and surgical treatment of perforated diverticulitis has been performed.

In 1000 cases, the following clinical presentations were found: mesocolic abscess in 139 patients, perisigmoid abscess in 288, generalized peritonitis in 355 and faecal peritonitis in 218.

Sixty-three patients were treated conservatively. The remainder underwent surgical treatment, which entailed diverting colostomy and drainage in 236 patients, Hartmann's operation in 398, colectomy with double colostomy in 39, exteriorization in 61, colectomy with

diverting colostomy in 50, or without diverting colostomy in 135, suture of perforation and drainage in 33, and drainage only in 12.

We have observed a statistically significant relationship between the clinical presentation and death ($P = 0.0001$), infection ($P = 0.0003$) and wound dehiscence ($P = 0.004$). There was no difference in mortality rate between treatment groups.

If recent cases are compared with earlier cases, a tendency to perform more Hartmann's operations now than previously, obtaining better results (particularly a reduction in infection rate), can be seen.

Management of ischaemic colitis

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The aim of this study was to review patients in our unit with ischaemic colitis. During the past decade 14 patients (five men and nine women) of mean age 67.5 (range 52–86) years presented with ischaemic colitis to our department; 21 per cent were treated as emergencies. The most common clinical symptoms were abdominal pain, diarrhoea and intestinal bleeding, whereas an increase in blood leucocyte count ($>10 \times 10^9 \text{ litre}^{-1}$) was the most common laboratory finding. Elective angiography was often diagnostic and modified the surgical operation. The lesions were located most frequently in the right and rectosigmoid colon. Thirteen patients required operative intervention with a mortality rate during the immediate postoperative period of 14.6 per cent. One patient was treated conservatively, with success. As the aetiology of ischaemic colitis varies, we stress its importance; it should be included in the differential diagnosis of patients with inflammatory bowel diseases as well as those with cardiovascular diseases. Early diagnosis of ischaemic colitis is of great value for the proper treatment of these patients.

Hartmann's procedure revisited

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The results of 37 consecutive cases of Hartmann's procedure over a 5-year period (1985–1991) were reviewed. The series consisted of 27 emergency procedures (11 diverticular disease, 13 carcinoma, two trauma and one sigmoid volvulus) and ten elective procedures (nine carcinoma and one peridiverticular abscess). The indications for emergency procedures were obstruction and perforation. All patients presented with faecal peritonitis owing to colonic perforation. The mean (range) age was 79.4 (34–90) years. The postoperative mortality rate was 30 per cent overall (11 of 37), 33 per cent (four of 12) in the diverticulitis group, 23 per cent (five of 22) in the carcinoma group, and 100 per cent in the iatrogenic trauma group. Death was mainly due to sepsis (82 per cent). Postoperative complications were mainly wound infections, which occurred in 43 per cent (16 of 37) of cases. In 25 per cent of the surviving patients, re-establishment of continuity was performed in three of 17 (18 per cent) of the carcinoma group and three of seven (43 per cent) of the diverticulitis group. No attempt at restoration of intestinal continuity was made in six cases due to medical risk in two, extensive carcinoma in two and local recurrence with metastatic disease in two. Three patients refused all further intervention. There were no postoperative deaths after the restoration of continuity. This series reflects the severity of the pathology in this high-risk group of patients. However, the operation can be life-saving for a selected group of patients and offers good palliation for advanced colorectal tumours.

Hartmann's procedure: extended indications in severe intra-abdominal infection

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Our experience from 98 Hartmann operations is presented. Over a 14-year period, 54 men and 44 women underwent emergency

Hartmann procedures for perforation and/or abscess due to diverticulitis (69 per cent), perforation and/or obstruction due to carcinoma (26 per cent), and miscellaneous causes (4 per cent). The mean age was 64.9 (range 22–87) years.

Ten patients died after operation (10 per cent). Sepsis and respiratory failure and wound infection developed in 57 per cent of patients.

Planned relaparotomies for severe intra-abdominal infection were performed in two patients, with no deaths. Colorectal continuity was subsequently restored in 56 patients (57 per cent).

In conclusion, it is suggested that this is an operation that is indicated particularly in left colon septic processes with severe peritoneal contamination.

Mechanically sutured colorectal anastomosis

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Mechanical sutures are widely used in our hospital for surgery of the digestive system, especially colorectal surgery.

From January 1987 to July 1989, 225 patients underwent operation for colonic pathologies of which 172 (76 per cent) needed some form of anastomosis. Of these patients, 100 were men (58 per cent) and 72 (42 per cent) women. Their mean age was 77 years. The colon was mechanically prepared for the operation and anticoagulant and antibiotic prophylaxis was applied. Elective surgery was carried out in 124 cases, and was urgent in 48. The predominant pathology was malignant while the rectosigmoid was the most frequent site with 108 cases (62 per cent).

The following surgical techniques were used: anterior resection in 75 patients, right hemicolectomy in 40, sigmoidectomy in 28, left hemicolectomy in 15, transverse colectomy in ten and complete colectomy in four. The overall morbidity rate was 31 per cent, with abscesses of the wall predominating (20 cases; 11 per cent). There were 12 fistulae (6.9 per cent), eight in elective cases and four in emergency cases. The operation most often complicated by fistula was anterior resection (nine cases). Repeat operation was only necessary in one patient.

In conclusion, colorectal pathologies, especially neoplasias, are most frequently found in the geriatric population. Antibiotic prophylaxis diminishes the risk of infections. The highest rate of morbidity is associated with emergency treatment in cases of neoplasia. Use of mechanical sutures shortens operation time, simplifying surgical techniques and reducing both the number and morbidity of fistulae.

Stapled colorectal anastomosis after primary Hartmann's procedure

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Stapled colorectal anastomosis is a widespread procedure. This study was undertaken to assess the efficiency of the method after a primary Hartmann's procedure. Over the period 1980–1991, 57 patients (36 men and 21 women; mean age 60 years) underwent stapled colorectal anastomosis; there were 11 poor-risk patients (American Society of Anesthesiologists grade 3). In 41 cases, an end-to-end anastomosis was performed after resection of the upper part of the rectal stump; end-to-side colorectal suture was made through the anterior rectal wall in 16 cases. Large cartridges (31 mm) could be used more often in the former cases (24 of 41) than in the latter (six of 16) ($P < 0.002$). In 12 patients, anastomosis had to be completed by some 'hand passed' stitches because of muscular tears caused by defective stapling. No diverting colostomy was performed. There was no postoperative mortality. No patient developed any clinical sign of anastomotic leak. Minor morbidity occurred in 19 cases, related mainly to pre-existing problems, or to defective wound healing. One patient required reoperation for intestinal obstruction and another patient for an incisional hernia. Median postoperative hospital stay was 12 days. Twelve suture lines were visualised by contrast enema; seven were described as wide and the others as narrow. Only two stenoses (both in the 28-mm group) were symptomatic and were successfully treated by endorectal dilatation. Restorative stapled colorectal anastomosis is a safe, although not always easy to perform, procedure, with low early and late complication rates.

Significance of air testing in stapled rectal anastomosis

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The aim of this prospective clinical study was to evaluate the usefulness of intraoperative air testing in detection of anastomotic leaks after the use of EEA staplers in rectosigmoid cancer. Twenty-one patients with rectosigmoid carcinoma underwent radical resection and continuity was established with an EEA stapler. The anastomosis was tested with air insufflation. Of these 21 patients with rectosigmoid carcinoma, ten (48 per cent) had low and 11 (52 per cent) had a high anterior resection. Four of the patients with low anterior resection had very low resection. The anastomosis was tested by intraoperative air testing in all patients and five (24 per cent) air leaks were detected. Anastomotic leak was detected in two of 11 patients who had a high anterior resection. In these two patients, after repair of small defects no further leaks were observed. Anastomotic leaks were detected by air testing in three of ten patients with low anterior resections. The defect was repaired with additional sutures. A proximal colostomy was performed in two patients with very low anterior resections and in one patient with low anterior resection. In all 16 patients with a negative air test, the doughnuts were complete. In the remaining five patients with a positive air test, the doughnuts were found to be complete in four. Clinical anastomotic leak was evident in only one of these patients. Intraoperative air testing is an easy, fast and reliable test in the assessment of the patency of stapled rectal anastomosis.

Multiple polypoid lipomatosis of the colon

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Among the benign tumours of the colon, lipomas represent a rare entity. These lesions are usually single, asymptomatic and located in the right colon. Multiple lipomas of the colon are uncommon; involvement of the whole of the colon, forming polyps of a great diversity of sizes (multiple polypoid lipomatosis of the colon), is even more unusual.

The case of a patient who was admitted with suspected colonic adenocarcinoma and familial polyposis is presented. He was found to have multiple polypoid lipomatosis of the colon.

Clinical characteristics, surgical aspects and the results of macroscopic and microscopic examinations of the resection specimen are analysed and the literature on multiple polypoid lipomatosis is reviewed.

Diverticular disease complicated by obstruction

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Obstruction secondary to diverticular disease is not very common, but the diagnostic and therapeutic problems can be very important. During the past 15 years, this clinic has observed 126 cases of diverticular disease: 72 patients were men, 54 women, of mean age 67 (range 36–88) years. Acute diverticulitis was present in 43.6 per cent, free perforation in 27 per cent, severe haemorrhage in 14.4 per cent and fistula in 5.5 per cent of cases.

Twelve (9.5 per cent) patients presented with obstruction caused by diverticular disease. A preoperative diagnosis of the diverticular nature of the obstruction was made in six patients who presented with pain and palpable mass in the lower left abdomen, fever and elevated white cell count. These patients also had a history of diverticulitis. Intensive medical therapy allowed improvement of the acute complication, confirmation of the diagnosis and elective surgical treatment. In the other six patients, preoperative diagnosis was not made, all these cases requiring emergency operation. Colonic resection was carried out in all 12 patients; immediate colorectal anastomosis was performed in the elective cases, while a Hartmann operation was preferred in emergency cases. Only in one of these was colonic resection with colorectal anastomosis performed, protected by a proximal colostomy. No postoperative deaths were observed.

This study confirms the difficult preoperative diagnosis of diverticular stricture; similar features to carcinoma are seen, which may also not be detected during operation. The necessity of resection in all cases, reserving immediate anastomosis for elective patients, should be stressed.

Mechanical (stapled) colostomy

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This study analyses a new method for creation of a colostomy. A total of 29 colostomies was made with the EEA stapler (US Surgical, Norwalk, USA) following Miles or Hartmann operations for cancer of the rectum or perforated diverticulitis. The complications included cases of stenosis (n = 2), partial dehiscence (n = 1) and peristomal ventral hernia (n = 3). A mechanical colostomy is certainly to be considered an operation of choice, owing to the low number of complications, reduction in surgical time, earlier restoration of function, better aesthetic result and slight cost difference.

Staples versus sutures for colonic anastomoses: a biochemical study in dogs

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Many studies have been published comparing staples and sutures for colonic anastomoses. Most have compared anastomotic strength and histological features. This study was performed to examine the concentration of hydroxyproline in the anastomoses. Mongrel dogs of both sexes were divided into three groups: six animals were controls (group 1); in 17 (group 2) a left hemicolectomy with stapled end-to-end anastomosis (EEA 25; Autosuture) was performed; in 17 (group 3) a left hemicolectomy with sutured end-to-end anastomosis was carried out using single-layer interrupted extramucosal 4/0 silk. The dogs were killed at 4, 7, 14 and 28 days after the operation. The concentration of hydroxyproline was determined by colorimetric techniques (Woessner) in the anastomoses and in other parts of the colon. We also performed clinical and histological studies. In the control group the concentration of hydroxyproline was 86 per cent in the transverse colon, and 115 per cent in the caecum compared with the left colon. The concentration of hydroxyproline in the anastomoses compared with the control group was:

	Time after operation (days)			
	4	7	14	28
Group 2	59.3	75.4	94.6	106.9
Group 3	62.2	87.9	90.2	99.3

Values are percentages

In conclusion, the concentration of hydroxyproline was not the same in all parts of the colon. The histological studies and hydroxyproline levels were similar in both anastomotic groups.

Double stapling technique for low colorectal anastomosis

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Since the introduction of the end-to-end anastomosis stapler for rectal reconstruction, this department has used a modification of the conventional technique in which the lower rectal segment is closed with the linear stapler (Reticulator 55; Auto Suture) and the anastomosis is performed using the premium CEEA (Auto Suture) instrument across the linear staple line. This 'double stapling technique' was used to perform low anterior resection for rectal tumours in 122 patients (68 men, 54 women) with a mean age of 65 (range 26–87) years. The rectal tumour was located between 6 and 13 cm from the anus. All patients were given prophylactic antibiotic cover. There was no perioperative death. Technical problems related to the stapling technique and requiring temporary colostomy occurred in one patient. The clinical anastomotic leak rate was 5 per cent (six patients) in two patients the fistula was treated successfully with a defunctioning transverse loop colostomy. Median hospital stay was

10.2 (range 6–23) days. Continence was normal in all patients at 6 weeks. One coloanal anastomotic stenosis required dilatation. The double stapling technique appears to facilitate low anterior resection of the rectum with safety, offering several additional advantages: (1) it obviates the placement of the distal purse-string and permits a lower anastomosis in some patients; (2) the rectum is not opened, which minimizes intraoperative contamination; and (3) it avoids the problem of disparity of sizes of the two ends of the bowel which may cause anastomotic complications.

Total colectomy with ileoanal anastomosis with a pouch in familial adenomatous polyposis

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Familial adenomatous polyposis, because of the associated risk of colon carcinoma, constitutes one of the major indications for total colectomy with ileoanal anastomosis with a pouch. This simultaneously abolishes the risk of malignancy and maintains the normal route of defaecation with acceptable functional results. We present eight cases (three women, five men) operated on by our surgical team from 1986 to 1991. The mean age was 47.6 (range 17–74) years. In two cases there was already carcinoma in the resected bowel (in one of them in two locations). We used a J pouch directly anastomosed to the anus without conservation of a rectal muscle cuff. We made a temporary ileostomy in only one case. There were no hospital deaths. The immediate postoperative morbidity rate was 37 per cent and consisted of intestinal obstruction (bands) (one case), peritonitis after the intraperitoneal dehiscence of an ileostomy (Weinberg style) (one case) and an abscess in the space of Retzius (one case). We are currently following up all patients, more than 6 months after the operation, to evaluate the functional results as follows: frequency of bowel movements during the day and at night, continence (faeces and flatus), soiling, faeces versus flatus discrimination, need for the use of antidiarrhoeal medications, need to use perineal pads, urinary and sexual dysfunction. To date we do not have any cases of pouchitis. We use total colectomy with ileoanal anastomosis with a pouch as the therapy of choice in familial adenomatous polyposis.

Functional results of coloanal anastomosis with reservoir

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The addition of a colonic reservoir to coloanal anastomosis has been suggested to compensate for the loss of the rectal reservoir, but the benefit of this procedure has not been adequately quantified. The aim of this prospective study was to assess the functional results of coloanal anastomosis with reservoir (CAAR) and to compare them with function in healthy controls. Functional results of 22 patients with CAAR were evaluated 8–26 months after colostomy closure and were compared with those of 36 healthy controls. The functional assessment involved daily frequency of stools, feeling of the need to defaecate, differentiation between flatus and faeces, flatus continence, and urgency and need for a pad. A score was used to express continence (normal, 1; minor leaks, 2; major leaks, 3) and the ability to evacuate (in one sitting, 1; in two sittings, 2; in three sittings, 3).

	Patients (n = 22)	Controls (n = 36)
Mean(s.d.) daily stool frequency	1.3(0.6)	1.2(0.6)
Desire to defaecate (n)*	21 (95)	35 (97)
Good differentiation (n)*	21 (95)	36 (100)
Good flatus continence (n)*	17 (77)	30 (83)
No urgency (n)*	22 (100)	29 (81)
No pad (n)*	19 (86)	36 (100)
Mean(s.d.) stool continence score	1.1(0.3)	1.1(0.4)
Mean(s.d.) evacuation score	1.6(0.7)†	1.0(0.1)

*Values in parentheses are percentages. †P < 0.01

The differences were not significant except for the ability to evacuate, which was worse in patients than in controls. In conclusion, these results suggest that CAAR provides nearly normal function with regard to stool frequency and continence, but results in some evacuation difficulties.

Abdominal irrigation with povidone-iodine in colorectal surgery

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The efficacy of intraoperative abdominal irrigation with a 1 per cent solution of povidone-iodine in preventing intra-abdominal infection and wound abscess in colorectal surgery was evaluated.

In all, 49 patients (29 men and 20 women), mean age 65.9 (range 28–95) years, were submitted to 50 operations. Fifteen procedures were performed as an emergency. Conditions predisposing to septic complications were present in 45 patients. All but four patients received short-term antibiotic prophylaxis.

According to the classification of Altemeier, 42 contaminated and eight dirty operations were performed: six patients (12 per cent) developed wound infection, one (2 per cent) developed an intra-abdominal abscess and two (4 per cent) had perineal infection after abdominoperineal excision of the rectum.

The results suggest that intraoperative irrigation with a 1 per cent solution of povidone-iodine decreases the incidence of postoperative infection in colorectal surgery for contaminated and dirty procedures.

Gardner's syndrome and desmoid tumours

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A study was recently performed on two patients (one man and one woman) who developed one of the less common complications of Gardner's syndrome: desmoid tumours arising from the abdominal wall and mesenteric root. Both patients underwent total proctocolectomy for polyposis coli in one with definitive ileostomy and ileoanal anastomosis with reservoir in the other.

Five years later, the woman underwent total resection of a desmoid tumour arising from the rectus muscle and mesentery of the small bowel. Radiotherapy was given after operation, and computed tomography every 6 months has shown no local recurrence for the past 2 years.

Three years after operation, the man underwent resection (which was incomplete for anatomical reasons) of a desmoid tumour arising from the rectus muscle and mesenteric root. Postoperative radiotherapy was refused by the patient. Computed tomography after 6 months showed extension of the tumour.

This report illustrates the difficulties in managing this disease and the aggressiveness of the histologically benign soft tissue complications. It appears that the nature of the desmoid tumour is not linked to malignancy of the colon polyps. We suggest that appropriate excision of the desmoid tumour with clear margins and postoperative radiotherapy could diminish the recurrence rate.

Prevention of leakage in hazardous intestinal anastomoses: an experimental study in rabbits

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The aim of this study was to prevent leakage from difficult intestinal anastomoses using collagen mesh. The biomaterials tested were glutaraldehyde and hexamethylene di-isocyanate crosslinked dermal sheep collagen (GDSC and HDSC), and processed porcine collagen (PPC). In 26 New Zealand White rabbits a low anterior resection was performed. Neither preparation of the intestine nor antibiotic treatment was used. The anastomosis (single layer inverting interrupted sutures) had a standardized leak of 3 mm. GDSC, HDSC and PPC were applied around the anastomosis in three groups of six rabbits, the fourth group being a sham-operated group ($n=8$). A Gastrografin (Schering, Burgess Hill, UK) enema was performed on the 14th day after operation. The study period was 3 weeks after operation.

In the sham-operated group, small covered paraintestinal infections were seen and one rabbit died of faecal peritonitis. Gastrografin enemas showed narrowing of all anastomoses with GDSC and HDSC; four and three rabbits, respectively, died of functional obstruction followed by stenosis. All rabbits in the PPC group had a good recuperation and their colons healed without stenosis. All bursting pressure measurements showed bursting outwith the anastomosis. Histology and microangiography showed excellent fibrovascular ingrowth and partial resorption of all biomaterials.

In rabbits GDSC and HDSC caused stenosis leading to functional obstruction after low anterior resections. PPC, on the other hand, seals small leaks and results in good healing of the intestinal anastomosis without stenosis.

Colorectal cancer

Morphometry and proliferative activity of colorectal adenomas as criteria of potential malignant transformation

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Most colorectal carcinomas arise from pre-existing adenomas. The risk of carcinomatous change correlates with adenoma size and histological appearance and influences the extent of endoscopic or surgical intervention. Morphometry and proliferative activity serve as further criteria of potential malignant transformation.

Eighty colorectal lesions (20 hyperplastic polyps (HP), 20 tubular adenomas (TA), 20 tubulovillous adenomas (TVA), 20 colorectal carcinomas (CA)), as well as biopsies of normal mucosa (MU), have been analysed morphometrically and histochemically. The following parameters were evaluated for the pedicle and crown of the adenomas: (1) the nuclear parameters of perimeter, area and shape factor (degree of circularity, 1.0 being a perfect circle), with morphometric image analysis; (2) silver-binding nucleolar organizing regions (AgNORs) which correlate with cellular activity; (3) proliferative activity with the monoclonal antibody Ki 67.

The morphometric analysis revealed the following mean(s.d.) nuclear areas: MU, 28(4.0) μm^2 ; HP, 32(6.4) μm^2 ; TA, 38(5.8) μm^2 ; CA, 48.8(5.2) μm^2 . The evaluation of the shape factors showed the following arrangement: MU, 0.7(0.22); HP, 0.62(0.05); TA, 0.61(0.06); TVA, 0.59(0.05). Carcinomas had the highest Ki 67 labelling rate as well as the most AgNORs, indicating that they have a significantly higher proliferative activity than the other specimens: CA>TVA>TA>HP>MU. Since the crown of the adenomas showed a higher Ki 67 labelling rate as well as higher AgNOR numbers than the pedicle, it is obvious that these regions differ in their proliferative activities.

Morphometrical analysis and evaluation of proliferative activity by these means makes possible a more precise analysis of tumour biology.

Azoxymethane-induced oxygen free radical activity in rat colonic carcinoma

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Oxygen free radical (OFR) activity has, among many effects, been implicated in carcinogenesis through DNA lysis. This study measured chemiluminescence and superoxide dismutase (SOD) inhibition as an index of OFR activity in azoxymethane-induced colonic carcinoma.

After 3 weeks' acclimatization, ten Fisher 344 rats were injected with azoxymethane (7 mg kg⁻¹ week⁻¹) over 10 weeks. All animals were killed at 37 weeks and colonic mucosa was sampled (5–25 mg wet weight) from sites of gross tumour (histologically confirmed), distant from tumour (3–5 cm) and from ten paired normal controls. The samples were processed in buffered luminol, and chemiluminescence (mV 100 mg tissue⁻¹) was measured in a luminometer. Each sample was then placed in a solution of SOD for 3 min before a second chemiluminescence estimation.

Colonic mucosa site	Chemiluminescence (mV 100 mg wet weight ⁻¹)		P*
	Before SOD	After SOD	
Control	8.1(1.0)	4.9(1.1)	<0.01
Remote from tumour	20.2(0.9)	6.7(0.7)	<0.001
Tumour	53.9(2.1)	11.0(0.8)	<0.001

Values are mean(s.e.m.). *Paired Student's *t* test

Chemiluminescence was significantly increased in azoxymethane-induced colonic carcinoma, both remote from and maximally at the tumour site, suggesting an OFR-associated field change.

Human herpes virus (cytomegalovirus, herpes simplex) in colorectal cancer

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Herpes simplex virus (HSV) and cytomegalovirus (CMV) in serum, urine, pharyngeal and tumour samples from patients submitted to surgery for colonic adenocarcinoma have been sought. This is to assess the epidemiological implications of these viruses in colorectal cancer.

Twenty-three patients operated on for colonic adenocarcinoma between January and May 1991 were studied. The mean age was 68.7 (range 55–82) years. Tumour sites where known were: left colon in seven cases, right in five, rectum in three, sigmoid in three and transverse colon in one. Dukes' classification was three A, six B, 11 C and three 'D'. On the day of the operation samples were collected from serum, urine, pharyngeal secretions and tumour tissue. A cell culture was performed, seeding the samples in a monolayer of MR-C and Vero cells in order to assess the cytopathic effects of HSV and CMV by direct observation. Specific monoclonal antibodies for HSV and CMV were also employed. Nucleic acid detection was performed by means of the dot blot, polymerase chain reaction and Southern blot techniques.

We have not been able to confirm the presence of HSV and CMV, either by means of cell culture or by the dot blot techniques, in the different types of samples from the patients studied. The detection of DNA from HSV and CMV using the dot hybridization technique has a lower sensitivity than the isolation of such viruses by culture. When a specific DNA probe is used, the sensitivity of the reaction is 10³ genomes (1–2 pg DNA).

Although our results have been negative, one cannot disregard the possible role of HSV and CMV in the pathogenesis of colorectal cancer. Further studies with more sensitive techniques are needed to confirm or refute the role of these viruses in colorectal cancer development.

Cytomorphometry as a prognostic indicator in colonic cancer

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Cytomorphometry has been evaluated as a simple prognostic technique in colonic cancer. It measures the main geometric parameters of the cell nucleus (area, minimum and maximum diameter and circumference) in ordinary histological specimens. Cytomorphometric parameter values were determined with a computerized system. Specimens were required to have high cellularity (at least 70 per cent), few inflammatory infiltrates and small areas of necrosis. The relationship of cytomorphometry to other parameters such as age, sex, stage (GITSG classification) and bleeding was examined in a study of intraoperative biopsies from 44 patients, comprising 23 men and 21 women (mean age 64 years) with right colon (34 per cent), left colon (11 per cent), sigmoid (39 per cent) and rectal cancer (34 per cent). The stage was B₁ in 14 per cent, B₂ in 43 per cent, C₁ in 9 per cent, C₂ in 28 per cent and D₁ in 6 per cent of these cases. Five patients presented with an occlusion and 33 with rectal bleeding. Univariate analysis showed that the stage and tumour site (*P* < 0.001) were significantly related to prognosis. The standard deviation of the maximum diameter (*P* < 0.01) and circumference (*P* < 0.02 with a negative correlation) were also related to survival. Multivariate analysis confirmed the significance of the standard deviation of the maximum diameter and the stage (*P* < 0.001). These parameters were then used to calculate the survival curves (Kaplan–Meier) and compared with Breslow's method. Cox's proportional risk model was used to evaluate survival. If due account is taken of the reservations concerning the reproducibility of the data offered by cytomorphometry and its high dependence on the skill of the operator, this technique can be used to aid the prognostic assessment of colorectal tumours.

Prognostic significance of tumour cells in the bone marrow of patients with colorectal cancer

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Despite radical tumour excision, almost one-half of all patients with colorectal cancer will suffer from local or distant tumour relapse. In order to detect 'occult' tumour cell spread, immunocytochemical techniques have been developed.

Bone marrow aspirates taken before surgery were tested by monoclonal antibody CK2, directed against the cytokeratin component no. 18, which is exclusively expressed in simple epithelia and malignant tumours deriving therefrom. After density centrifugation the antibody reaction was developed by an alkaline phosphatase technique.

In 28 of 88 patients (32 per cent) undergoing resection of primary colorectal cancer, CK⁺ (cytokeratin component no. 18-containing) cells were found in the bone marrow aspirates. Cells were found in none of 102 patients without malignant disease. During the observation time (median 35 (range 12–58) months) the cumulative relapse-free survival rate (Kaplan–Meier analysis) in patients showing CK⁺ cells in the bone marrow aspirate was significantly poorer ($P = 0.009$) than those without CK⁺ cells in the marrow.

By means of a stepwise regression analysis, CK⁺ cells were clearly shown to be an independent predictor of tumour relapse ($P = 0.003$), as well as of tumour penetration beyond the muscularis ($P = 0.040$), involvement of regional lymph nodes ($P = 0.026$), poor histological differentiation ($P = 0.010$) and male sex ($P = 0.001$), but of neither age, nor rectal or colonic localization.

Although none of our patients developed manifest bone metastases, we have shown that immunocytochemically detected tumour cells in preoperative bone marrow aspirates are an important and independent prognostic factor for disease-free survival in patients with colorectal cancer. Possibly, this new determinant of risk can be used to select early stage patients, who are likely to benefit from adjuvant therapy.

Detection of circulating tumour cells in colorectal cancer

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Metastasis is the result of a sequence that begins with the local invasion of blood and lymphatic vessels by tumour cells and culminates in their extravasation into the host organ. Some of these cells subsequently proliferate and develop into secondary deposits. The metastatic process is recognized as being inefficient, although reliable quantitative estimates of the circulating tumour cell burden in human cancers are lacking. This study was designed to detect and quantify circulating tumour cells in preoperative peripheral blood samples from patients with colorectal cancer.

A combined conventional cytological and immunohistochemical approach was used to identify tumour cells in the mononuclear cell layer of blood after density gradient centrifugation. Forty-four patients were examined, two of whom had overt liver metastases.

Malignant cells were detected in six patients (Dukes' B, two; Dukes' C, four) at concentrations ranging from 100 000 cells ml⁻¹ in one of the patients with liver metastases to 40 cells ml⁻¹ where there was no evidence of dissemination. One patient, with a tumour cell concentration of 800 cells ml⁻¹, has subsequently developed recurrent disease in the pelvis and liver metastases. Of five patients with circulating tumour cells who underwent resection for cure, only one had evidence of extramural vascular invasion.

This study demonstrates that the haematogenous spread of tumour cells is detectable before operation, and thus precedes handling of the tumour. The identification of such cells may occur in the absence of metastatic disease, including lymph node deposits, and histological evidence of vascular invasion.

Preliminary audit of a regional colorectal cancer register

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In January 1990 a regional colorectal cancer register was commenced serving a population of 1.5 million. Demographic, clinical and

pathological data on all newly diagnosed cases of colorectal cancer were recorded using a computerized database to provide accurate information for future clinical research.

There were 805 histologically confirmed new cases in 18 months. Clinical information was available on 656 patients: 355 (54 per cent) were male and 301 (46 per cent) were female. Of the patients 38 (5.8 per cent) were under 50 years of age and 400 (60.1 per cent) were in their seventh or eighth decades at presentation. There were 399 (62.5 per cent) colonic tumours and 239 (37.5 per cent) were rectal. Surgery was performed on 641 (97.7 per cent) patients and 15 (2.3 per cent) had biopsies only. There were 528 (82.5 per cent) elective and 112 (17.5 per cent) emergency procedures. A total of 458 (71.6 per cent) was judged curative and 182 (28.4 per cent) were palliative. Adjuvant therapy was offered to only 37 (5.7 per cent) patients. The overall hospital morbidity rate was 7.2 per cent (47 patients), 5.9 per cent for elective and 10.7 per cent for emergency operations. In-hospital mortality rate was 5.2 per cent (34 patients), 4 per cent for elective and 10.7 per cent for emergency procedures.

These figures confirm that this region has one of the highest incidences of colorectal cancer worldwide. The data also reveal a relative decline in the proportion of rectal cancer. The register is useful for research and for future resource planning.

Human leucocyte antigen expression on colorectal adenocarcinoma and its association with DNA ploidy

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Among the factors influencing prognosis in patients with solid tumours, human leucocyte antigen (HLA) expression and DNA content are two cellular parameters which seem to be associated with the prognosis and the degree of differentiation of solid tumours.

We examined HLA expression and DNA content using flow cytometry in 48 specimens from patients with colorectal adenocarcinoma. Cell preparations were obtained from samples of tumours and from colorectal mucosa (control). The HLA expression was tested using the monoclonal antibodies W6/32 (anti-class I), B8.12.2 (anti-class II) and HLe1 (anti-CD45) to measure leucocyte infiltration of tumour. Propidium iodide was added to the single cell preparations to stain DNA and a cytometer FAScan was used.

Of the tumours, 50 per cent were aneuploid (DNA index 1.21–1.89). Of the colorectal mucosa samples studied, 100 per cent showed positive expression to anti-class I and 86.6 per cent to anti-class II. In tumour samples compared with controls HLA class I expression was reduced in 53.2 per cent, while HLA class II expression was increased in 38.5 per cent. Low HLA class I expression was never found in association with a concomitant relatively high HLA class II expression. Low HLA class I expression was observed in 57.1 per cent of aneuploid tumours.

Our data suggest that the regulatory pathways which control HLA expression of cellular tissue components are unaffected by the process causing neoplastic transformation. Changes of HLA expression may represent an important parameter in prognostic evaluation and progression of colorectal adenocarcinoma.

Multifactorial and regression analysis of prognostic factors in cancer of colon, rectum and anal canal

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Between 1977 and 1987, 394 patients with colorectal cancer were submitted for curative resection. All the patients were followed up for 2 years.

A regression analysis of 18 independent prognostic factors was made to assess the contribution of each factor to overall survival. The factors analysed were: age, bloody stools, change in bowel habits, abdominal pain, duration of symptoms, synchronous tumours, metachronous tumours, family history of cancer, tumour size, macroscopic classification, Union Internacional Contra la Cancrum (UICC) and Dukes' classification, venous invasion, lymph node invasion, adjacent organ invasion, extension of lymph node dissection, grades of differentiation and postoperative adjuvant therapy. These factors were grouped into 49 prognostic possibilities.

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The statistics program used was STATPRO. Value of adjustments was tested by Fisher's exact test and was highly significant ($P < 0.01$). After finding the regression coefficients and their significances, we were able to perform an analysis of the variables and establish the following ranking order of prognostic significance for cancer of the colon and rectum: venous invasion ($P < 0.001$), grade of differentiation ($P < 0.01$), invasion of adjacent organs ($P < 0.01$), UICC staging ($P < 0.05$), lymph node involvement ($P < 0.05$), age ($P < 0.05$), Dukes' classification ($P < 0.05$).

Increasing incidence of proximal colorectal cancer

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We have recently set up a colorectal cancer register in our region. All patients with histologically proven colorectal cancer were included in a computerized database. In the first year (1990) there were 487 cases of colorectal cancer for a population of 1.5 million. The site distribution of tumours showed an unexpectedly high proportion of proximal lesions and a correspondingly low proportion of rectal cancers. When compared with figures available for the same region 12–14 years earlier, a significant difference was observed.

Site	1976–1978	1990
	n	n
Right colon	292 (23.5)	237 (48.7)
Left colon	339 (27.3)	119 (24.4)
Colon unspecified	59 (4.8)	0 (0.0)
Rectum	551 (44.4)	131 (26.9)
Total	1241 (100.0)	487 (100.0)

Values in parentheses are percentages. $P < 0.00001$ ($\chi^2 = 123$, 3 d.f.)

Experience for the first 6 months of 1991 confirms a continuing low proportion (27 per cent) of rectal tumours. These results demonstrate a highly significant proximal shift in the site distribution of colorectal cancer over the last two decades. This proximal shift has been noted in other areas where there is a high incidence of colorectal cancer and has major clinical implications. In particular, full colonoscopy rather than flexible sigmoidoscopy would be needed for any future screening programme.

Endorectal ultrasonography in staging small rectal tumours

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Careful staging of small tumours could contribute to accurate evaluation and may influence therapeutic choice. Among 80 rectal neoplasms assessed before operation by endorectal ultrasonography (EUS) (Aloka SSD 520, 7.5 MHz), 31 were suitable for local excision. There were 18 villous adenomas (group 1) and 13 invasive cancers (≤ 3 cm in diameter) (group 2). In group 1, preoperative biopsies displayed a benign pattern in 16 cases and, in two more cases, small nests of carcinoma within the villous tissue. All these patients underwent local excision. In group 2, patients had a local excision (11), or a radical resection (two) as a result of the staging (N_1 tumours). Tumours were classified by EUS as uT_1 , T_2 or T_3 , according to Hildebrandt, and the results were compared with the pathological specimens. Tumours of group 2 were classified as uT_1 in 14 cases and uT_2 in four cases. One uT_1 tumour was understaged (T_2). Invasive cancer was found in three of the uT_2 tumours, and deep inflammatory changes in one. Tumours in group 2 were classified as uT_1 (two), uT_2 (eight) and uT_3 (three). Two T_3 tumours were understaged. Lymph nodes were identified in five cases and tumour invasion was confirmed by two radical resections. Early perirectal recurrence in one of the three cases treated by local excision probably confirms the initial staging. Search for lymph nodes was negative in eight cases. One lymphatic recurrence developed, confirmed by radical resection. Four patients were free of disease mean (range) 18 (10–30) months later. Follow-up is too short as yet in three cases. With respect to the discrimination between T_1 and $T_{2/3}$

tumours and between $T_{1/2}$ and T_3 tumours, the positive predictive values were 93.3 per cent and 100 per cent respectively. The negative predictive values were 93.7 per cent and 92.8 per cent. Such a score helps decide local excision of benign lesions and superficial cancers (T_1 , T_2). Evaluation of the method with respect to lymph node involvement is difficult because there were few patients and no systematic radical resection. Positive predictive values and negative predictive values approximated 75 per cent and 80 per cent respectively. In our series, EUS could prevent the surgeon from performing a curative local excision in as many as five of 13 cases.

Role of intrarectal ultrasonography in preoperative evaluation of rectal cancer

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Manual rectal examination and intrarectal ultrasonography (IRUS) were used in the preoperative staging of 13 patients with rectal carcinoma, and the accuracy compared with pathological staging. The accuracy of the degree of tumour infiltration with manual rectal examination was 77 per cent, but nodal status could not be determined. The accuracy of IRUS on the degree of tumour infiltration was found to be 100 per cent. Of the ten patients in whom nodal examination was possible, IRUS staging was correct in three. IRUS understaged in five patients and overstaged in two. It is concluded that IRUS is useful in the preoperative staging of patients with rectal carcinoma, especially when tumour invasion is concerned. Determination of the nodal status with IRUS is dependent on the experience of the ultrasonographer and the accuracy may improve as experience is gained.

Endoluminal ultrasonographic accuracy in rectal cancer

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The aims of this study were to evaluate the accuracy of endoluminal ultrasonography (ELU) in staging local tumour spread and lymph node involvement in rectal cancer and to establish the role of ELU in the postoperative follow-up of patients with rectal cancer. From 1986 to October 1991, 214 patients with rectal cancer, located between 2 and 16 cm from the anal verge, were studied before operation with ELU. All these patients underwent surgery: local excision, anterior resection and abdominoperineal resection were performed in 16, 159 and 39 cases respectively. Pathological findings were compared with preoperative ultrasonographic images obtained by a radial probe with a 7-MHz transducer. Of 214 patients, six and seven cases were understaged and overstaged respectively, resulting in an accuracy of 93.9 per cent with regard to tumour status. In patients who underwent major surgery (198 cases), the accuracy of this method in evaluating lymph node status was 84.3 per cent, due to 31 incorrectly staged patients (26 false positive and five false negative). Results obtained in the postoperative follow-up (with 58 recurrences detected by ELU of 335 patients studied, and ten of 18 asymptomatic patients reoperated upon) stress the importance of routine use of ELU for early detection of extraparietal asymptomatic local recurrences.

Accuracy of endosonography in the staging of rectal cancer before and after preoperative radiotherapy

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Between January 1988 and October 1991, 31 patients with rectal cancer were evaluated by clinical staging (31) and endorectal sonography before (29, one complete stenosis) and after (29) radiotherapy. Two criteria were correlated with histological findings: tumour confined to the rectal wall or spread beyond it, and the presence of mesorectal lymph node involvement.

The 29 patients who underwent endorectal ultrasonography before radiotherapy were staged as uT_2 (four cases), uT_3 (23 cases) and uT_4 (two cases). Fifteen days after irradiation, endorectal ultrasonography showed a regression of the tumour in all cases; the uT stage was different in 13 patients, and in one case there was a

change in the uN stage. Comparison of the preoperative clinical and echographic assessment of local invasion beyond the rectal wall with postoperative histopathology revealed a correlation with digital examination after radiotherapy in 16 of 27 patients with palpable tumours, with endorectal ultrasonography before irradiation in 16 of 29 staged tumours and with endorectal ultrasonography after irradiation in 21 of 28 staged tumours. The presence of mesorectal lymph node involvement determined by histological examination correlated with the results of endorectal ultrasonography after radiotherapy for 17 of 26 staged tumours.

Endorectal ultrasonography provides a good assessment of the tumour stage before irradiation. This stage should be considered for survival studies. Radiotherapy altered the endosonographic staging of rectal cancer.

Clinical result of transanal endoscopic microsurgical treatment of rectal neoplasms

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The transanal endoscopic microsurgical (TEM) technique has been used in clinical practice since 1983. From January 1986 to the present, 324 patients underwent TEM. Of these, 229 suffered from adenomas, 88 from carcinomas and a few from various diseases such as carcinoid tumours, rectal diverticula or ulcer simplex.

The use of a special 40-mm rectoscope and stereo-optics allows close resection of tumours with a three-dimensional view. All patients were prepared as for major colonic surgery: bowel lavage and single-dose antibiotic prophylaxis at induction were routine.

All grades of dysplasia were found in the group of patients with adenoma. During follow-up, only seven recurrences, all treatable by means of snare resection, were found. Of carcinoma patients 62 per cent suffered from pT₁ low-risk tumours. This stage and grade of the disease form the main reason for referral for TEM. In this group of patients the recurrence rate at follow-up was 4 per cent.

The mean hospital stay was 10 days. Postoperative pain was considerably less than after conventional surgery. TEM is an effective method that allows the surgeon to operate on rectal tumours without laparotomy and provides benefits to patients suffering from benign neoplasms and early cancers of the rectum.

Abdominoperineal excision of the rectum without transfusion and with primary closure of the perineal wound

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Blood loss and hypovolaemic shock have been shown to affect the immune system significantly¹. A higher rate of tumour recurrence and increased susceptibility to infectious complications associated with perioperative transfusion has also been demonstrated².

We analysed prospectively the data of patients undergoing synchronous abdominoperineal excision of the rectum for cancer in order to assess if such major surgery was feasible without transfusion, while obtaining primary healing of the perineal wound. Synchronous abdominal and perineal operation was conducted with meticulous haemostasis; complete suture of the perineal wound (pelvic peritoneum, levator ani, fat and skin) was combined with suction drainage in all cases.

We studied 20 patients. The median age was 66 (range 48–80) years. There were 16 American Society of Anesthesiologists (ASA) grade II patients, three of grade III and one of grade IV. Three patients had Dukes' B tumours and ten had Dukes' C tumours. One patient had metastases. The median operation time was 240 (range 200–420) min. Four patients required blood transfusion (of 1, 1, 2 and 4 units). There were no deaths. All perineal wounds healed primarily with no wound infection.

In conclusion, extensive abdominoperineal excision with a minimal amount of transfusion and with primary closure of the perineal wound can be performed in unselected patients with cancer of the rectum.

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Perioperative mortality in colorectal carcinoma surgery

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Colorectal adenocarcinoma is one of the commonest malignant neoplasms in Europe. In Spain it is presently the second most common cancer.

We have undertaken a retrospective study of 250 cases during the period 1980–1990. Patients were divided into two groups according to age; the first comprised 119 patients aged under 70 years with a mean(s.d.) of 57.3(0.7) years and the second group consisted of 83 patients aged over 70 years with a mean(s.d.) of 77.2(0.5) years. Preoperative assessment included clinical evaluation, chest radiography, colonoscopy and liver ultrasonography.

Analysis of results was by a computer statistics program. Symptoms were present in 95 per cent of cases. Tumours located in the rectum were the most prevalent in this study (47.4 per cent), followed by those in the sigmoid colon (23.2 per cent). Dukes' B and C tumours were the most prevalent (B, 45 per cent; C, 41 per cent). Perioperative mortality rate was 6.9 per cent for the first group and 16.2 per cent for the second group. In elective surgery the global perioperative mortality rate is 10 per cent, reaching 20 per cent in emergency surgery.

Diagnosis of colorectal carcinoma used to be delayed because of the absence of early symptoms. The perioperative mortality rate is higher in more elderly patients and in emergency surgery.

Value of tumour markers in colorectal cancer

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We evaluated the usefulness of tumour markers in the prediction of early local recurrence and hepatic metastases. In 100 patients with colorectal carcinoma entered in this study, preoperative determinations of carcinoembryonic antigen (CEA), monoclonal antigen CA 19-9, α -fetoprotein (AFP), γ -glutamyl transpeptidase (GGT) and phosphohexose isomerase (PHI) were performed. Tumours were classified into Dukes' A, B, C and 'D'. Postoperative tumour marker levels were determined 30 days after operation. Follow-up was performed every 3 months by tumour marker analysis, rectocolonoscopy with biopsy, hepatic ultrasonography and chest radiography. Statistical analysis was by the Kruskal–Wallis test and Mann–Whitney U test.

Our results show a poor correlation between levels of preoperative markers and Dukes' classification. In patients with hepatic metastases the tumour markers were higher, with the exception of AFP (CEA: 790(40); CA 19-9: 98(20); GGT: 75.3(20) and PHI: 200(40)). Mathematical study of these data and ultrasonographic examination could predict liver metastases. These data suggest that follow-up of colorectal carcinoma with tumour marker monitoring may predict early liver secondaries and increase diagnostic sensitivity and specificity.

Prognostic markers for colonic and rectal carcinomas

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The identification of prognostic factors in colonic or rectal cancer is useful as information to the patient and in selection for adjuvant therapy. In this study we analysed the adjusted survival of 236 patients with colonic ($n = 104$) and rectal ($n = 132$) cancer who underwent curative resection between 1966 and 1988. Complete follow-up was obtained in all patients and, in each group, we correlated survival and the following clinicopathological factors: age, sex, duration of symptoms, presence of intestinal obstruction, tumour site, depth of tumour penetration, lymph node status, grade of differentiation, lymphocytic infiltration, type of invasive margin, mucin production, venous and lymphatic invasion. Cumulative 5-year survival rate was 59 per cent in patients with colonic cancer and 52 per cent in those with rectal cancer (P not significant, Mantel–Cox test). The resulting multivariate analysis using a Cox stepwise model showed a significantly lower survival rate in the presence of lymph node involvement and intestinal obstruction in the colonic carcinoma

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group, and lymph node metastases, greater depth of penetration, venous invasion, scant lymphocytic infiltration and poorly differentiated tumour in the rectal cancer group. Our data suggest that colonic and rectal carcinomas have different prognostic markers and, therefore, need separate criteria for selection of patients for adjuvant therapy.

Combined preoperative radiation therapy and sphincter-preserving resection in distal carcinoma of the rectum

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In an attempt to maintain sphincter function in patients treated for low rectal carcinoma we decided to combine preoperative radiation therapy with very low anterior resection. Feasibility and results were assessed in a prospective study.

From January 1987 to December 1990, 42 consecutive patients having an adenocarcinoma (T₂ or more) palpable *per anum* were included in the study. The mean (s.d.) age was 66(12) (range 35–85) years. Radiation therapy (30–35 Gy) was delivered on a sacral field in ten fractions over a 12-day period. Surgery was performed 2 months later. Eight patients whose residual tumour remained very low had to undergo abdominoperineal excision.

In 34 patients (81 per cent) a conservative rectal resection with very low stapled anastomosis was performed. Their cancers were initially located at a mean (s.d.) distance of 55(13) (range 30–80) mm from the anal margin. A diverting colostomy was performed in 13 patients. Minor anastomotic leakage was observed in three patients. Functional results were good in all but two patients. With a median follow-up of 38 (range 8–58) months, three local recurrences were observed. At 3 years the overall and disease-free survival rates were 90 and 81 per cent respectively.

Our study demonstrates that most patients with low rectal carcinoma can be safely managed using preoperative radiation therapy combined with sphincter-preserving resection.

APACHE II score in the evaluation of risk in patients with colorectal cancer: comparative study between patients under and over 70 years of age

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A number of systems has been evaluated to quantify surgical risk, but none has gained widespread usage. This study evaluated the APACHE II score as a predictor of risk.

The study included 212 patients undergoing elective surgery for colorectal cancer in the period from January 1987 to June 1991. Patients were evaluated before operation and risk factors were corrected where possible. All patients received preoperative chest physiotherapy and prophylactic antibiotics; low molecular weight heparin was given when indicated.

There were 88 patients aged less than 70 years (mean 58 years) and 124 patients were over 70 years old (mean 77 years). The APACHE scores, incidence of complications and surgical mortality are shown in the *Table*.

	APACHE score				
	0	I	II	III	IV
Patients under 70 years					
No.	3	57	22	6	—
Complications	0	23	15	5	—
Deaths	0	0	1	2	—
Patients over 70 years					
No.	—	49	56	19	—
Complications	—	24	28	18	—
Deaths	—	3	2	8	—

The source of risk was mainly respiratory in the younger group, and cardiovascular in the older patients. Increasing risk score was

associated with an increased incidence of complications, but this trend did not reach statistical significance. However, the risk score did define a group at statistically higher risk of postoperative death ($P = 0.05$).

The APACHE II score has been able to define a group of patients at high risk of postoperative morbidity and mortality. These patients deserve particular attention before operation.

Factors affecting mortality and morbidity rates following colorectal surgery in the elderly

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In an attempt to identify factors affecting morbidity and mortality rates in colorectal surgery in elderly patients, 27 patients (15 men and 12 women) of mean age 77 (range 66–95) years have been studied. The colorectal operation was for malignancy in 25 cases and for benign disease in two.

Nine patients had emergency procedures. Preoperative assessment by the American Society of Anesthesiologists (ASA) criteria showed: ASA grade I, one patient; ASA grade II, 18 patients; ASA grade III, seven patients; ASA grade IV, one patient. All patients received short-term antibiotic and antithromboembolic prophylaxis.

The mortality rate was 7 per cent (two of 27) and the morbidity rate was 33 per cent (nine of 27). Mortality and morbidity rates were correlated mainly with the presence of severe systemic disease and with emergency operations. Mortality and morbidity rates were respectively: zero of one and one of one in the ASA grade I group, zero of 18 and five of 18 in the ASA grade II group, one of seven and three of seven in the ASA grade III group, one of one and zero of one in the ASA grade IV group. Mortality and morbidity was one of nine and five of nine in emergency procedures and one of 18 and three of 18 in elective operations.

We believe that age is not a contraindication to colorectal surgery, but careful preoperative assessment should become an integral part of the evaluation of these patients.

Influence of allogeneic and autologous blood transfusion on infectious complications after colorectal cancer surgery: results of a prospective randomized trial

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Several retrospective studies indicate an adverse effect of allogeneic blood transfusion on the recurrence rate of neoplasms and the rate of postoperative infectious complications. A prospective randomized study was performed in 424 patients with colorectal carcinoma to investigate whether autologous blood transfusions can abrogate this putative allogeneic blood transfusion effect. Patients randomized to the autologous group had to donate 2 units of blood before surgery. Transfusion rules were standardized and were the same for both groups. This predeposit blood donation programme resulted in a decrease of 142 (40 per cent) allogeneic blood transfusions in the autologous group compared with the allogeneic group. In the allogeneic group 118 of 212 (56 per cent) patients needed blood transfusion, whereas in the autologous group only 59 of 212 (28 per cent) patients needed additional allogeneic blood transfusion. Therefore the number of patients exposed to allogeneic blood transfusion was decreased by 50 per cent.

Infectious complications were seen in 111 patients (26 per cent). Wound infection occurred in 8 per cent, urinary tract infection in 7 per cent, pneumonia in 3 per cent and intra-abdominal infections in 7 per cent of the patients. Two patients, both with metastatic disease, died from their infectious complications. In the allogeneic group 51 (24 per cent) patients had infectious complications compared with 60 (28 per cent) patients in the autologous group (P not significant).

Comparing the infected with the uninfected patients showed no influence of age, sex, preoperative haematocrit, type of operation and Dukes' classification on the rate of infectious complications. Significantly greater blood loss was measured in the group of infected patients ($P < 0.005$). Of the 271 patients who received blood transfusion, 82 (30 per cent) developed infectious complications compared with 29 (21 per cent) of the 141 untransfused patients

($P < 0.05$). The infected patients received a higher mean number of blood transfusions compared with the uninfected group (3.0 versus 1.6, $P < 0.0005$).

In conclusion, blood loss and blood transfusion seem to be risk factors for postoperative infectious complications that cannot be avoided by replacing allogeneic blood transfusion by autologous blood transfusion.

Sandostatin inhibits the growth of two animal models of colorectal liver metastases in the rat

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The treatment of colorectal liver metastases remains poor, the majority of patients dying within 1 year of diagnosis. Two models of liver metastases have been developed which reliably produce hepatic tumour after intraportal (IP) inoculation of tumour cell lines and the effects of the somatostatin analogue Sandostatin (Sandoz, Camberley, UK) on the growth and development of metastases have been investigated.

After IP injection of 1×10^7 K12/Tr cells (an adenocarcinoma of colonic origin syngeneic to the BD IX rat), or 4×10^6 HSN cells (a fibrosarcoma syngeneic to the Hooded Lister (HL) rat), groups of 12 rats received subcutaneous injection of either Sandostatin, 2 µg twice daily, or saline (control) for 3 (HL rats) or 4 (BD IX rats) weeks. There was a significant reduction ($P < 0.001$, Mann-Whitney U test) in the percentage hepatic replacement of hepatic tumour in the Sandostatin-treated groups compared with controls: in BD IX rats, median 0.6 (range 0–2.5) per cent; controls, 17.5 (5.7–24.2) per cent; and in HL rats 2.7 (0–26.5) per cent; controls, 76.4 (56.3–85) per cent. The reduction in the growth and development of both types of tumour was associated with a marked stimulation of hepatic reticuloendothelial system activity and a decrease in liver blood flow compared with controls, offering an explanation, at least in part, for the mechanism of action of the somatostatin analogue.

These results indicate that Sandostatin significantly inhibits the progression of hepatic tumour in two animal models of liver metastases and may be of benefit in the treatment of hepatic metastases in humans. Further studies are required to evaluate this hypothesis.

Stoma care in patients after excision of the rectum

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Rectal excision burdens the patient with a permanent colostomy. This causes a change in the patient's lifestyle and has important psychological effects. The colostomy can be managed by means of irrigation, with or without the use of an obturator.

A total of 245 patients with a permanent left iliac fossa end colostomy was evaluated in terms of social status, adaptation to stoma, complications and the use of irrigation.

The mean (s.d.) age was 64.9 (5.0) years; 64 per cent were men; 11 per cent had a university degree; 50 per cent had an elementary degree; and 75 per cent were married.

In 53 per cent of patients the stoma has influenced lifestyle: 45 per cent of patients reported restriction of sexual activity, 44 per cent an effect on employment status, and 8 per cent altered family life. Adaptation to the presence of a stoma required 6–12 months.

The technique of stoma irrigation was known to 61 per cent of patients, but practised by only 25 per cent. Those patients using irrigation had fewer problems than those who did not, as shown in the Table.

	Irrigation (%)	No irrigation (%)	P^*
Borborygmi	24	76	<0.0001
Flatus	28	72	<0.0001
Skin irritation	24	76	<0.0001
Stoma bag detachment	5	95	<0.0001
No adaptation	8	92	<0.0001
Stoma problems	13	87	<0.0001

Irrigation is an effective method of managing a permanent colostomy. It reduces the frequency of stool passage, the number of bags used and the amount of flatus passed. Comfort is improved.

A few patients used an obturator, but it was not found to be effective.

Colorectal cancer in patients under 40 years of age

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There is controversy as to whether patients under 40 years of age suffering from colorectal cancer constitute a subgroup different from older patients. To investigate this problem, data from all patients operated on over a 20-year period were retrospectively analysed. Patients < 40 years old (group 1) were compared with those of 40 years or older (group 2).

Of all patients ($n = 1876$) operated on for primary colorectal cancer from 1971 to 1990, 4.7 per cent (89) belonged to group 1. In the younger patients, higher proportions of right-sided colonic tumours (30 per cent, $n = 27$ versus 19 per cent, $n = 344$), of mucinous carcinomas (33 per cent, $n = 29$ versus 17 per cent, $n = 310$) and of multiple synchronous carcinomas (11 per cent, $n = 10$ versus 4 per cent, $n = 65$) were found. Additionally, advanced tumours (Dukes' 'D') were more frequent in the younger patients (35 per cent, $n = 31$ versus 21.8 per cent, $n = 390$). Accordingly, radical resection was possible in only 63 per cent (56) of patients in group 1 but in 73 per cent of group 2. Overall actuarial 5-year survival rate (not corrected for age) was 45.5 per cent and 44.7 per cent for groups 1 and 2 respectively. Following radical (R_0) resection the corresponding figures were 73.0 per cent and 59.8 per cent. Median survival after R_1/R_2 resection was 5 months in group 1 and 8.5 months in group 2.

Patients < 40 years of age showed different site distribution of colorectal tumours, worse tumour characteristics and more multiple carcinomas. Prognosis, at least after R_0 resection, nevertheless was as good or even better than that for the older patients. Early diagnosis and radical surgery appear to be the most important factors at any age.

Colorectal carcinoma in patients younger than 40 years of age

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Fifty patients younger than 40 years of age with colorectal carcinoma who were surgically treated at this department between 1979 and 1989 are evaluated in this retrospective study.

These cases constituted 15 per cent of the total number of patients undergoing operation for colorectal cancers (332 patients) in the same period. The mean age was 30.9 (range 10–39) years and the male:female ratio was 1.5:1. A family history of colorectal carcinoma was found in seven patients (14 per cent). Of the tumours, 72 per cent (36 patients) were located in the rectosigmoid and 28 per cent (14 patients) in the proximal portions of the colon. All tumours were adenocarcinomas. Mucinous adenocarcinomas were found in 22 of the 50 patients under 40 years (44 per cent) and in 57 (21 per cent) of the 275 patients older than 40 years. The average survival time for the first group was only 21 months. The most common symptoms at first admission were haematochesia (72 per cent), weight loss (54 per cent), abdominal pain (42 per cent) and changes in bowel habits (34 per cent).

In this study, young patients with colorectal cancer had a poor prognosis.

Value of follow-up after curative resection of colorectal cancer

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Between 1980 and 1990, 159 patients aged 75 years or less underwent curative resection for colorectal cancer in our department. Patients were followed up for 5 years (3-monthly for 2 years, then every 6 months). They were routinely assessed by physical examination, measurement of carcinoembryonic antigen level, chest radiography, abdominal ultrasonography and endoscopy. In selected cases computed tomography and bone scan were carried out.

Colorectal cancer

Operable recurrent disease was detected in 12.5 per cent of patients (8.2 per cent local recurrence, 3.1 per cent liver metastases and 1.9 per cent lung metastases). A curative resection was possible in only 5 per cent of patients.

The sensitivity and specificity of the various investigations in the detection of recurrent disease has been assessed. In spite of the low yield of curable recurrent disease, we feel that intensive follow-up is justified.

UCL 41.2: a new monoclonal antibody to colorectal cancer

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Although several monoclonal antibodies have been used in the radioimmunolocalization of colorectal cancer, there remains a need for more monoclonal antibodies with good reactivity and specificity to this disease.

Using a crude membrane extract prepared from several colorectal cancer specimens as immunogen, a new monoclonal antibody has been generated to colorectal cancer. Reactive spleen cells from immunized BALB/c mice were fused with the myeloma cells, NSO. Reactive antibodies were identified by means of an enzyme-linked immunosorbent assay using the immunogen as the target antigen. Immunohistochemistry revealed five antibodies which reacted with colorectal tissues. One of the antibodies, UCL 41.2, reacted with over 90 per cent of different colorectal cancers. Although it also reacted with the epithelia of the gastrointestinal tract, bile duct and gallbladder, it did not react with hepatocytes, kidney, spleen or lung cells. Fluorescent activated cell analysis showed strong binding of UCL 41.2 with a colonic cancer cell line LS174T but no binding with peripheral blood lymphocytes. Using a cell lysate of LS174T as target antigen, Western blotting revealed that the molecular weights of protein recognized by UCL 41.2 were 40, 80 and 120 kDa, which were different from the control anticarcinoembryonic antigen monoclonal antibody A5B7 which reacted with a protein of 200 kDa. An Ouchterlony assay showed that UCL 41.2 belongs to the immunoglobulin G_{2b} subclass. These findings confirm the suitability of UCL 41.2 in the radioimmunolocalization of colorectal cancer.

Interferon alpha and fluoropyrimidines: *in vivo* effects as single agents or in combination in colonic cancer

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Adjuvant therapy after colonic resection for cancer is still of limited benefit; 5-fluorouracil (5-FU) and derivatives remain the best choice when indicated. Recently, preliminary clinical findings have shown objective responses using a combination of interferon alpha (IFN- α) and 5-FU in advanced colorectal carcinoma.

A synergistic effect between IFN- α and the prodrug 5'-deoxy-5-fluorouridine was previously observed *in vitro*. A murine model was developed to determine the therapeutic potentialities of IFN alone or combined with fluoropyrimidines. The tumorostatic effect of IFN- α on xenografts of the WiDr colon cell line in nude mice is reported. Using this *in vivo* model, the synergistic effect of IFN- α and the prodrug 5'-deoxy-5-fluorouridine at clinically achievable doses of both drugs was confirmed.

The clinical application of this combination of drugs should be investigated, particularly the new fluoropyrimidines which appear to have more specificity towards cancer cells and thus fewer adverse effects.

Efficacy of interleukin 2 and 5-fluorouracil in the treatment of metastatic colorectal carcinoma

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Adoptive immunotherapy of renal cell carcinoma and melanoma has shown promising results; however, little is known about the efficacy of immunochemotherapy in metastatic colorectal cancer.

Twenty-five patients, age range 25–71 years, with irresectable metastatic colorectal carcinoma were treated with cyclical interleukin 2 (IL-2) and 5-fluorouracil (5-FU). Each cycle of treatment lasted 28 days. On days 1–5, IL-2 was infused via a central venous catheter at a dose of 3×10^6 Cetus units m^{-2} day^{-1} . On days 7, 14 and 21, 5-FU was given as a bolus at a dose of 600 mg m^{-2} . A maximum of six cycles was given. The most common side-effects were pyrexia and rigors. No patient required intensive care. Response was measured radiologically at 2, 4 and 6 months.

	No. of patients (n = 25)
No response	17 (68)
Stable disease	3 (12)
Partial response	2 (8)
Full response	3 (12)

Values in parentheses are percentages

The overall response rate of 20 per cent is similar to that obtained in other tumours treated with adoptive immunochemotherapy.

Reconstruction of a continent neoeanus in patients with low rectal carcinoma

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The presence of an end colostomy continues to be a major disability for patients who require rectal excision. To avoid a stoma, a neoeanus operation was performed between 1989 and 1991 in ten patients with carcinoma of the distal third of the rectum. The tumour was located at a distance of <2.5 cm from the upper margin of the subcutaneous part of the external anal sphincter (EAS) in six patients (group 1). In four patients (group 2) the distance of the tumour from the upper margin was >2.5 cm, but insufficient to perform a low anterior resection.

In group 1, after excision of the anorectum, a neoeanus was constructed according to the method of Schmidt using a double seromuscular layer approximately 6.5 cm in length. In group 2, the subcutaneous part of the EAS was preserved; otherwise the reconstruction was identical.

There was no mortality or serious morbidity, and no faecal soiling in either group. Frequency of defaecation was good in group 1, with a stool frequency of three to four per day. However, excellent continence has been achieved by the modification of the original Schmidt operation in group 2 patients, with a daily stool frequency of one to two.

Schmidt's neoeanus operation with the preservation of the subcutaneous part of the EAS can be recommended as a useful reconstructive operation in patients who would otherwise need abdominoperineal excision of the rectum.

Adjuvant immunotherapy with Rubratin of postoperative patients with colorectal carcinoma: a randomized phase III trial

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Rubratin is the cell wall preparation of *Nocardia rubra* and shows immunoactivating efficacy in preclinical and clinical studies. A trial was carried out after surgery in colorectal cancer patients divided into lymph node-positive and -negative groups. Both groups were randomized into Rubratin or control subgroups. Patients in the control group received no further treatment; patients in the Rubratin group received the drug monthly for up to 1 year after surgery.

More than 220 patients have been recruited with 90 evaluable patients in the lymph node-negative group (median observation time 52 weeks) and 36 patients in the lymph node-positive group (median observation time 25 weeks). Patients treated with Rubratin showed the following toxicities: local (induration, ulceration, etc.) (30 per cent); fever (9 per cent); nausea or vomiting (3 per cent). In five of 67 patients the treatment had to be discontinued due to toxicity; 19 patients required a dose reduction.

The evaluation of response is preliminary: in patients without lymph node involvement Rubratin is beneficial; 2.1 per cent of them relapsed compared with 14.9 per cent of the control group. In the lymph node-positive group 36.4 per cent of the patients relapsed compared with 14.3 per cent in the control group. Irrespective of these results, it has to be stated that the number of patients and the observation period is still insufficient.

Survival after resection of locoregional recurrence of colorectal cancer

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During a 15-year period (1975–1991), 76 patients (40 men and 36 women, mean age 61 years) underwent resection of locoregional recurrence of colorectal cancer. The 76 patients were evenly split between rectal and colonic cancer. A total of 87 lesions was resected, nine patients having more than one site of recurrence. The mean interval between the initial operation and locoregional recurrence was 23 months. The site of recurrence was anastomotic (i.e. endoluminal) in 29 patients, perianastomotic in 39, distal in four and pelviperineal in four (i.e. after abdominoperineal resection). Twenty-six of the recurrences were asymptomatic (15 anastomotic), but only three of these were detected by an isolated increase in carcinoembryonic antigen level.

Curative resections were performed in 49 patients. Resection was extended in 31 patients, including five liver resections. Six patients (8 per cent) died in hospital; mortality rate was significantly ($P < 0.03$) higher in those who underwent palliative resection. One or more postoperative complications were found in 21 patients. Half of the patients had adjuvant therapy.

Mean(s.d.) overall actuarial 5-year survival rate was 29(7) per cent. Factors apparently affecting mean(s.d.) survival, but not achieving statistical significance were site of primary (colon 44(12) per cent, rectum 15(6) per cent) and sex (women 45(12) per cent, men 12(6) per cent). Factors significantly influencing survival were curative versus non-curative resection (47(10) versus 0 per cent at 31 months; $P < 0.001$); site of recurrence (anastomotic 43(12) versus 24(1) per cent; 0 per cent for other sites; $P > 0.01$); and asymptomatic versus symptomatic recurrence (41(12) versus 24(7) per cent; $P < 0.05$).

These results suggest that surgery is the only curative treatment of locoregional recurrence of colorectal cancer and that it can be performed with acceptable mortality and morbidity. Survival is better for locoregional recurrence of colonic cancer, anastomotic recurrences and asymptomatic patients. Adjuvant therapy may improve these results.

Results of surgery in patients with two or more colorectal tumours

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Between 1963 and 1991, 1899 patients have been operated on for colorectal carcinoma. Two or more tumours were found in 116 (6.1 per cent) patients, in whom 256 carcinomas were found; 73 (62.9 per cent) patients had synchronous and 46 (39.6 per cent) had metachronous tumours. Three (2.6 per cent) had a synchronous and metachronous colorectal carcinoma.

In total, 183 operations have been carried out. In 166 cases of synchronous carcinoma, 25 extended colorectal resections and 64 standard resections were performed. In 90 cases with two metachronous tumours, seven extended and 83 standard colorectal resections were performed. Two patients had inoperable carcinomas.

Comparing patients with double and those with multiple carcinomas, the 5-year survival rates were 66 and 64 per cent respectively following curative surgery. After subdivision by tumour stage and comparing synchronous and metachronous multiple carcinoma, no difference was seen in the survival rate.

These results suggest that operative intervention in all tumour stages is appropriate in patients with multiple tumours. The timing of the incidence (synchronous or metachronous) is unimportant as is the extent of the operation. The survival rate depends on the stage but not on the multicentricity of the tumour.

Accurate preoperative diagnosis of a double or multiple carcinoma and regular postoperative follow-up is recommended.

Colonic carcinoma associated with Crohn's disease

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It is now generally recognized that patients with long-standing Crohn's disease have an increased risk of developing colonic cancer. This risk is estimated to be four to 20 times that of the general population. The mean time between onset of disease and carcinogenesis is 20 years.

We report a case of a 48-year-old man who presented 19 years earlier with Crohn's disease with multiple rectoperineal fistulae. In 1987, a rectourethral fistula developed and was successfully managed by a transverse colostomy. The patient was readmitted to hospital in 1989 with severe weight loss and sepsis resulting from a buttock abscess. Blood tests showed an elevated carcinoembryonic antigen level. Barium enema revealed neoplastic stenosis of the excluded sigmoid colon and rectum. At laparotomy, the tumour proved to be irresectable because of peritoneal carcinomatosis, and the patient died 8 months later. Pathology showed a combined mucinous and signet ring cell carcinoma.

Colonic carcinoma associated with Crohn's disease has various characteristics differentiating it from sporadic cases of colonic cancer. The mean age of diagnosis of cancer is 49 years for patients with Crohn's disease; that is, 10 years younger than that of cancer in the general population. There is a tendency for cancer to develop in inflammatory bowel strictures, excluded bowel loops, stumps and fistulae, as well as in the right colon. Two or more tumours are found in over 10 per cent of cases and epithelial dysplasia is common. There is a high prevalence of mucinous adenocarcinoma (50 per cent) compared with sporadic occurring colonic tumours (9 per cent). The prognosis appears no worse than that of colonic cancer in the general population when patients are matched for Dukes' classification. Unfortunately, diagnosis is usually made late in the course of the disease when patients are no longer amenable to surgical treatment.

Regular colonoscopy is recommended in patients with long-standing Crohn's disease to detect colonic cancer at a treatable stage.

Recurrence of carcinoma of colon and rectum: symptomatic versus asymptomatic patients

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Retrospectively, we have analysed the results of surgery for recurrence of carcinoma of colon and rectum. All recurrences were operated on by us during the period 1985–1990. The aim of the study was to evaluate the likelihood of performing 'curative' re-resections for this type of cancer. After primary resection, follow-up was performed every 4 months during the first year and then every 8 months. History, physical examination, alkaline phosphatase, haemoglobin and carcinoembryonic antigen were recorded at each visit. Barium enema, colonoscopy, ultrasonography and computed tomography were included in some cases. Thirty-one patients were diagnosed to have recurrence and underwent reoperation. Initial Dukes' classification was A 3.2 per cent ($n = 1$), B 48.4 per cent ($n = 15$) and C 48.4 per cent ($n = 15$). Clinically, at the time of recurrence, there were two groups: asymptomatic patients (AP; $n = 12$) and symptomatic patients (SP; $n = 19$).

	AP	SP	P
Mean(s.d.) age (years)	62.9(9)	62(10)	n.s.
Dukes' classification			n.s.
A	0	1	
B	7	8	
C	5	5	
Surgery			<0.15
Palliative	7	15	
'Curative'	5	2	
Not known	0	2	
Topography			n.s.
Rectum	6	9	
Colon	6	10	
Mean(s.d.) time between operation (months)	21(10)	25(27)	n.s.

n.s., Not significant

Colorectal cancer

The survival rate at 15 months after recurrence was 43 per cent for 'curative' surgery *versus* 29 per cent for palliative surgery, with no statistical differences. In conclusion, the possibility of a 'cure' after surgery for recurrence of carcinoma of the colon and rectum is low. The diagnosis of recurrence in asymptomatic patients does not improve the final results.

Generation of human monoclonal antibodies from colorectal diseases

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Hybridoma techniques enable a direct examination of human antibody response to colorectal cancer and inflammatory bowel conditions through immortalization of regional lymph node lymphocytes. However, unlike the production of mouse monoclonal antibodies, the generation of human monoclonal antibodies has met with considerable difficulties because of the uncertainty of the presence of reactive lymphocytes, low cell fusion frequency, low immunoglobulin secretions by hybrids, and unstable clones. There are only a few reports of human monoclonal antibodies to colorectal diseases.

Human lymphocyte hybrids have been generated using lymphocytes obtained from lymph nodes draining colorectal cancer and inflammatory bowel conditions from 59 patients. The lymphocytes

were stimulated with pokeweed mitogen and fusions were performed with two human lymphoblastoid cell lines (LICR-LON-HMy2 and UC729-6) using polyethylene glycol and an electrofusion technique. Fusion products were plated into 6578 wells with the formation of 2018 hybrids. A crude membrane extract prepared from several colorectal cancers was used as the target antigen to screen for membrane reactive antibodies by means of an enzyme-linked immunosorbent assay (ELISA).

Reactive antibodies were identified from 15 hybrids (a yield of 0.7 per cent). Further characterization was performed by means of fluorescent activated cell analysis against live cells. Eight antibodies with strong reactivity to colonic cancer cell lines were found. Their reactivity with other cancer cell lines was tested. These included breast, bladder, cervical, uterine, small cell lung cancer, pancreatic, hepatoma, epitheloid, nasopharyngeal, T cells, monocytic and erythroblastoid cells. With a few exceptions, the five antibodies obtained from patients with colorectal cancer did not react with other cell lines. In contrast, the three antibodies obtained from patients with inflammatory bowel conditions showed more cross-reactivity with other cell lines. None of the antibodies reacted with either phytohaemagglutinin-stimulated or non-stimulated peripheral blood lymphocytes. ELISA shows that these antibodies belong to the immunoglobulin M class. Some of the hybrids have been cloned a few times and continue to secrete antibodies.

These results show that there is an antibody response to human colorectal cancer and inflammatory bowel conditions and that stable human-human hybrids can be produced to 'capture' these humoral responses.

Duodenum and small bowel

Surgical treatment of duodenal rupture

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We have retrospectively studied the results of treatment of retroperitoneal rupture of the duodenum.

Between 1976 and 1990, 450 patients were operated on because of trauma to abdominal organs. Five patients (four men and one woman aged from 28 to 52 years) had ruptured retroperitoneal duodena. All patients were intoxicated with alcohol when injured.

The patients reached hospital 2–17 h after the trauma. One patient had isolated abdominal trauma; the others had multiple injuries (head, chest, limbs). Clinical symptoms and abdominal paracentesis data were indications for operation.

After hospitalization four patients underwent operation within 2 h; one patient who had serious head and chest trauma was operated on after 38 h because of wrong interpretation of abdominal paracentesis data. Retroperitoneal duodenal rupture was diagnosed in all patients at operation.

In two patients the injury was localized in the vertical part and in three patients in the horizontal part of the duodenum.

Retroperitoneal duodenal suture and retroperitoneal drainage was performed for two patients, both of whom died. One of these patients died because of anastomotic leakage and infection; the other, operated on after 38 h in very poor condition, died during operation. Duodenal suture, gastroenterostomy, pyloric suture or retroperitoneal drainage was performed in three cases; these patients recovered.

Because traumatic duodenal rupture is frequently followed by anastomotic leakage, it is desirable to exclude the passage of food in the postoperative period.

Wilkie's syndrome: a report of 16 cases

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Five men and 11 women with Wilkie's syndrome were treated surgically at this institution from 1971 to 1981. The median age was 31.9 (range 16–47) years. Diagnosis of Wilkie's syndrome was always confirmed by upper gastrointestinal radiology and by the intraoperative findings showing extrinsic obstruction of the third part of the duodenum. All patients underwent an operation that we have called 'intestinal derotation'.

The caecum and the ascending colon are mobilized. Medially this procedure reaches the posterior fold of ascending mesocolon as far as the base of the mesentery and, superiorly, frees the secondary attachments of the right-hand segment of transverse mesocolon. The second and third parts of the duodenum are drawn by their adherences to the right end of the transverse colon and extensively mobilized in their posterior aspects. The secondary root of the mesentery is detached from the ileocaecal junction to the point of emergence of the superior mesenteric vessels. Division of the posterior parietal peritoneum at the duodenojejunal flexure and dissection of the ligament of Treitz complete the mobilization of the duodenum. The duodenal loop can now be turned 270° clockwise, below the mesenteric root.

After surgical treatment, relief of symptoms was achieved in all cases. No early postoperative complication occurred. All patients were followed up at 5 and 10 years; obstructive symptoms had always completely disappeared, all patients had gained weight, and an upper gastrointestinal series demonstrated a regular duodenal shape, while the dilated proximal duodenum had become normal.

Surgical treatment of duodenal diverticula

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Fourteen patients with duodenal diverticula, comprising nine men (64 per cent) and five women (36 per cent), were treated at this

institution from 1976 to 1991. Their mean age was 56.1 (range 42–63) years. The second part of the duodenum was involved in ten cases (71 per cent), the third in three cases (21 per cent), and the fourth in one (7 per cent). Multiple diverticula were found only in two of the three cases located in the third segment. In those patients with diverticula in the second part, the main symptoms were colicky abdominal pain in four cases, recurrent episodes of cholangitis in two cases, epigastric discomfort, pain, distension and vomiting in two cases, haemorrhage in one case and progressive jaundice in one case. In those patients with diverticula of the third and fourth part, vomiting was the main symptom. Barium meal findings were those of radio-opaque pouches for diverticula of the second and fourth part, and significant stenoses in those of the third part. Diverticula of the second part of the duodenum were treated by simple resection in four cases. In five cases a transduodenal sphincteroplasty was also performed. In one case these two procedures were complemented by a duodenojejunal bypass. Two cases of diverticula of the third part required resection of the duodenal segment, while the third one and the only diverticulum located in the fourth part were simply resected. The postoperative course was uneventful in all cases. Those ten patients undergoing operations before 1986 were followed up 5 years after operation. One had died from an unrelated disease, while the remaining nine had fully recovered from the operation.

Duodenal diverticula and bacteriobilia

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Duodenal diverticula (DD) usually manifests as inflammation of the DD wall owing to retention of contents or complications of gallstone disease and secondary pancreatitis.

The aim of this paper is to demonstrate the relationship between DD and bacteriobilia, and the development of secondary pancreatitis and cholangitis.

Surgery was performed on 13 of 22 patients with DD revealed by radiographic examination. Patients were examined for bacteriobilia and diverticulitis. Simultaneous operations (cholecystectomy, sphincteroplasty, drainage of pancreatic abscess and resection of DD) were carried out in 11 cases; in one case the pancreatic main duct was reimplanted into the duodenal wall, and in one a separate resection of DD was performed because of constant complaints after elective cholecystectomy 1 year previously.

Bacteriobilia (*Escherichia coli*, *Staphylococcus epidermidis*, *Bacillus proteus*, *Streptococcus anhemolyticus*) was discovered in nine of 13 cases. Inflammation of the DD wall was found in all of these patients, although the microflora in bile and DD was identical in only six cases. A suture line dehiscence occurred in one patient with fatal results. Diverticulitis was observed in only one of four patients with sterile bile.

On the grounds of our clinical experience, prophylactic antibiotic therapy should be recommended before surgical treatment of inflammatory DD. In elderly patients the operation of choice may be gastrointestinal bypass.

Cardiorespiratory morbidity during gastrointestinal endoscopy

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We have studied cardiorespiratory changes in patients undergoing upper endoscopy and colonoscopy to determine the nature of, incidence of and risk factors for defined cardiorespiratory events. Significant events were defined as: oxygen saturation <90 per cent (by pulse oximetry), systolic blood pressure <100 mmHg, electrocardiograph (ECG) rhythm changes, pulse <50 min⁻¹ or >100 min⁻¹. Patients were monitored before sedation, for 5 min after sedation, during endoscopy and for 10 min after the procedure.

Endoscopy was performed on 133 patients. In 19 examinations (ten colonoscopies), cardiorespiratory events occurred after sedation. In 35 of 60 upper endoscopies and 57 of 73 colonoscopies, significant events were recorded during the procedure.

	Upper endoscopy (n = 60)	Colonoscopy (n = 73)
Oxygen saturation <90 per cent	16	26
Blood pressure <100 mmHg	8	18
ECG rhythm changes	12	10
Pulse <50 min ⁻¹	2	7
Pulse >100 min ⁻¹	12	15

Cardiorespiratory morbidity was significantly more common during upper or lower endoscopy in the 48 patients with a history of cardiac disease ($P < 0.01$, Fisher's exact test). During 11 oesophageal stricture dilations, all nine patients with a previous cardiac history developed ventricular ectopic beats ($P = 0.007$).

This study points to risk factors for cardiorespiratory morbidity during gastrointestinal endoscopy.

Eighty cases of Meckel's diverticulum

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We report 80 patients with Meckel's diverticulum seen over a 40-year period. In this series, Meckel's diverticulum was found in 2 per cent of the total number of patients undergoing laparotomy. The greatest number were seen in patients under 20 years of age (48 patients) and in those over 50 years of age (13 patients).

The clinical diagnosis is rather difficult. Meckel's diverticulum may produce haemorrhage, inflammation and obstruction in children and young adults. Obstruction of the small intestine in a patient presenting with fever and who has undergone appendectomy could be another form of presentation of Meckel's diverticulitis. In our series Meckel's diverticulum has produced inflammation in 38 patients, obstruction in 23 and haemorrhage in three patients. The surgical treatment was the removal of the Meckel's diverticulum by local excision (50 patients) or segmental resection of the small intestine (30 patients). Two deaths occurred.

Laparoscopic treatment of small intestinal obstruction

The Belgian Group for Endoscopic Surgery

During a 4-month period, 31 patients (mean age 53 years) were explored by laparoscopy for small intestinal obstruction (SIO). Acute SIO was present in 24 patients (group 1) and chronic SIO in seven patients (group 2).

In group 1, 19 patients had undergone previous abdominal surgery. Gas insufflation was performed using a Verres needle in 16 and open laparoscopy in eight cases. The mean delay between SIO and surgery was 3-8 days. Ten patients (42 per cent) were successfully treated by laparoscopy (nine single band, one incarcerated crural hernia) without mortality or morbidity. The mean postoperative stay was 6-2 days. Fourteen patients (58 per cent) were converted to laparotomy. The reasons were intestinal injury (five), colonic cancer (one), intestinal ischaemia (three), dubious diagnosis (three), technical problem (two). Postoperative complications included one parietal abscess and one prolonged postoperative ileus. The mean postoperative stay was 17 days.

In group 2, six patients had undergone previous abdominal surgery. Gas insufflation was performed using a Verres needle in three and open laparoscopy in four cases. Five patients (71 per cent) were successfully treated and two patients (29 per cent) were converted to laparotomy for intestinal injury. There was no mortality or morbidity and the mean postoperative stay was 4-4 days.

In conclusion, successful laparoscopic treatment of SIO was obtained in only 48 per cent of patients. In acute SIO, the best results were obtained when a single band was present. In chronic SIO, the best results were obtained when the small intestine was not dilated. Open laparoscopy is the safer technique for gas insufflation.

Multiple symmetrical lipomatosis: diagnostic and surgical strategy

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The authors report 12 cases of multiple symmetrical lipomatosis (LMS) treated over a 5-year period: diagnosis and therapy are described. Hospitalization in 11 patients was for a functional reason, whereas only one patient required surgery for cosmetic reasons.

Investigations included laboratory blood tests, radiography, ultrasonography and computed tomography to elucidate the extent of the masses. In seven patients, muscle biopsy revealed mitochondrial dysfunction which is still under investigation. There were eight cases of alcohol abuse; seven patients displayed hypertriglyceridaemia and four hyperuricaemia. The lipomas were cervically located in all the patients; in one, a paravertebral extension produced dyspnoea and hindered cervical movement; in another, the oesophagus was displaced by the lipoma.

Surgery included total removal (with or without liposuction), total removal in more than one operation because of the extension of the masses, and partial removal at the patient's request or because of the involvement of important structures.

This study suggests that LMS should be considered as a systemic disease: for this reason diagnosis should be in the light of several types of investigation and various surgical options must be considered.

Malignant tumours of the small bowel

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Fifty-five cases of malignant tumours of the small bowel were operated on between 1 January 1960 and 31 December 1990. There were 34 men and 21 women with a median age of 52 years. Histology showed a lymphoma in 15 cases (27 per cent), an adenocarcinoma in 12 cases (22 per cent), a metastasis in 11 cases (20 per cent), a carcinoid tumour in ten cases (18 per cent) and a leiomyosarcoma in seven cases (13 per cent). The tumour was revealed by a complication in 34 per cent of the cases. Surgical treatment was performed as curative in 27 cases (49 per cent) (more or less extensive resection) and palliative in 27 cases (49 per cent) (resection or internal diversion); a simple biopsy was made in only one case (2 per cent). Mortality rate during hospitalization was 14 per cent (eight cases) without any change with time; it was 4 per cent for curative treatment and 22 per cent for palliative surgery which is often done for advanced lesions. The 5-year survival rate was 18 per cent (ten cases).

Malignant tumours of the small bowel are rare and of bad prognosis, for their diagnosis is difficult and late; their treatment is palliative in half the cases.

Continuous monitoring of postoperative small bowel motility after different surgical procedures

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In a prospective trial, small bowel motility was evaluated in patients who underwent diagnostic laparotomy or gastrectomy. The aim was to determine whether postoperative small bowel atony is dependent upon the type of surgery. A three-tip transducer, with transducer distances of 15 cm was placed, during operation, via a needle catheter jejunostomy 80 cm below the angle of Treitz into the jejunum. The intraluminal pressure was measured continuously three times per second for 140 h after surgery. Data were recorded on a memory card and were processed by a personal computer program.

Group A consisted of three patients who underwent exploratory laparotomy for inoperable gastric cancer, while group B consisted of eight patients who underwent gastrectomy for gastric cancer. A migrating motor complex (MMC), the normal interdigestive motor pattern of the small bowel, was not detectable in any of the 11

patients for the first 18 h after operation. In group A the MMC appeared after a mean(s.d.) of 24(4.5) h and in group B the MMC was detectable after 82(25) h. The duration of the MMC was normal in both groups and the mean(s.d.) interval between MMC appearance was 98(21) min in group A and 95(35) min in group B. The mean(s.d.) progression velocity was $4.2(1.1) \text{ cm s}^{-1}$ in group A and $2.0(1.2) \text{ cm s}^{-1}$ in group B.

The results of the present study strongly suggest that duration of small bowel atony depends upon the type of surgery. The delayed progression velocity after extensive surgery may be a reason for decreased nutrient absorption in these patients.

Effects of protein on healing of jejunal anastomosis in rats subjected to total parenteral nutrition

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Skin and fascial healing have been extensively studied, and the results have long been considered to be equally applicable to less homogeneous tissues such as the gut. However, recent studies have suggested that gastrointestinal healing differs from skin and fascial healing in a number of aspects. Perhaps because small bowel anastomoses clinically offer fewer complications than in the colon, the healing process in this part of the gastrointestinal tract has been little studied. On the other hand, nutritional factors are known to play an important role in wound healing.

In the present study we evaluated bursting pressure of jejunal anastomoses, and studied its relation to the components administered in parenteral nutrition. Sixty Wistar rats (260–300 g) of both sexes were divided into two groups according to diet (30 protein deficient and 30 with excess protein). The animals were randomly killed on the fourth, seventh and 11th days after operation. The determinations on day 4 in particular provided data on the degree of inflammatory response and mucosal healing; day 7 revealed intensity of collagenization; by day 11 a normal macroscopic appearance was expected – albeit with persisting histological alterations. The left jugular vein was cannulated to infuse the diet at a rate of 2 ml h^{-1} . A 1-cm segment of jejunum was then excised, followed by terminoterminal anastomotic reconstruction using 5/0 monofilament polypropylene. Anastomotic bursting pressure was determined at different times after surgery. The segment was then opened longitudinally, and the perimeter of the burst zone determined with a micrometer. The radius was subsequently determined by the formula: radius = perimeter/ 2π .

This gave parietal bursting tension (PBT) according to Laplace's law: $\text{PBT (dynes)} = 1.33 \times 10^3 \times \text{bursting press.} \times \text{radius}$ (see Table).

	Protein deficient	Protein excess	P
Day 4	0	0	—
Day 7	0.70(0.03)	0.63(0.03)	n.s.
Day 11	0.80(0.05)	0.93(0.02)	0.03

Values are mean(s.d.) expressed in newtons. n.s., Not significant

Jejunal anastomoses were found to lose strength during the first 3 days after surgery, owing to diminished capacity to resist bursting. Strength increased over days 4–7, in parallel with the collagen-forming period. By day 11 there were significant differences in anastomotic resistance between the two groups. Similarly, other authors have correlated protein depletion with diminished traction resistance; protein deficiency prolongs inflammation and reduces collagen synthesis.

Effects of colchicine on the formation of peritoneal adhesions in the rat

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The aim of this study was to evaluate the influence of colchicine on the formation of adhesions in experimental peritonitis.

Peritonitis was induced in male Wistar rats by intraperitoneal injection of a suspension of magnesium silicate in hydrochloric acid (pH 1.6). Colchicine, $35 \mu\text{g}$ per kg body-weight, was administered orally daily over a period of 5 weeks. A solution of 0.9 per cent sodium chloride (1 ml orally) was used as a control. Evaluation of the development of adhesions was performed weekly for 5 weeks after the experiment. The study included macroscopic evaluation of the area and the location of the adhesions, their microscopic features (staining by van Gieson method) and the biochemical structure of collagen. Crosslinks were analysed using high pressure liquid chromatography (HPLC).

It was found that the area and size of the adhesions of animals treated with colchicine was much smaller than those of controls, especially after the third week. Histopathological examination of adhesions of the colchicine group showed a lower intensity of fibrosis and a smaller diameter of collagen fibre bundles than in the control group. Quantitative measurement by HPLC showed a diminished number of interchain crosslinking forms of collagen.

This animal study suggests that colchicine diminishes the area and intensity of fibrosis. This drug has an influence on collagen biosynthesis, and produces collagen bundles smaller in diameter.

Phytobezoar obstruction of the intestine: a late complication of gastric surgery for peptic ulcer

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The incidence of mechanical bowel obstruction by a phytobezoar was sought in patients who had been subjected to gastric surgery for peptic ulcer. A total of 227 patients with intestinal obstruction was included in the study, 23 of whom had undergone operation for peptic ulcer disease. Although the phytobezoars caused obstruction in only 4 per cent of the total series, they accounted for obstruction in six (26 per cent) of the 23 patients, comprising a sevenfold increase in risk. All patients presented with the clinical signs of small bowel obstruction. The ileum was the site of obstruction in five. The types of gastric operation in the six cases were truncal vagotomy and drainage in two, subtotal gastrectomy in two, and truncal vagotomy and antrectomy in the remaining two. All four resections were accompanied by Billroth II anastomosis. The offending foodstuffs were beans in four patients; local fruit (*P. lauricerasus*) and orange pulp caused obstruction in the other two. The average interval from gastric surgery to intestinal obstruction was 13 years. Phytobezoars should be considered in the aetiology of mechanical intestinal obstruction in any patient referred with symptoms and signs of intestinal obstruction and a history of previous gastric surgery.

A clinical study of complication predictive indices in digestive tract surgery

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With the aim of determining the value of clinical and nutritional parameters in predicting the development of complications after surgery, a prospective clinical trial involving 75 patients undergoing major digestive tract surgery was carried out.

Forty-two different parameters were monitored before operation, including anthropometric values, biochemical, immunological and

Parameter	Cut-off point	Sensitivity (%)	Specificity (%)	Accuracy (%)
MAC male (cm)	<24	47	85	74
MAC female (cm)	<22	33	92	86
AMA male (cm^2)	<42	46	79	70
AMA female (cm^2)	<31	33	92	86
Quick index (%)	<88	44	86	77
Albumin (g dl^{-1})	<3.3	44	86	77
Prealbumin (mg dl^{-1})	<17	50	86	79
Transferrin (mg dl^{-1})	<195	44	85	76
Transfusion (units)	≥ 3	25	98	83
Operation time (min)	≥ 210	31	97	83

clinical data such as diagnosis, length of surgical procedure, and amount of blood transfused around the time of operation.

Significant statistical values were found for middle arm circumference (MAC) and arm muscular area (AMA) as anthropometric parameters; for the Quick index, creatinaemia, serum levels of albumin, prealbumin and transferrin as biochemical indices; for the number of units of perioperative blood transfused; and for the time taken for the surgical procedure.

For each parameter, cut-off points were determined, at the point where the true and measured prevalences were similar.

A step-wise discriminant analysis was performed to obtain two multiparametric predictive functions. One involved nutritional parameters (surgical risk nutritional index, SRNI), and the other clinical and nutritional parameters (surgical risk clinical and nutritional index, SRCNI). These two formulae were derived:

SRNI:
$$Z = (0.07 \text{ (Quick)}) + (0.07 \text{ (PRE)}) + (0.04 \text{ (AMA)}) - 9.5$$

SRCNI:
$$Z = (0.1 \text{ (Quick)}) + (0.04 \text{ (PRE)}) + (0.05 \text{ (AMA)}) - (0.02 \text{ (T)}) - (0.27 \text{ (TB)}) - 7.95$$

where Quick is the Quick index as a percentage; PRE is prealbumin concentration (mg dl⁻¹); AMA is arm muscular area (cm²); T is time in surgery (min); and TB is units of transfused blood.

If Z < 0, a high complication rate after operation is likely; if Z > 0, a low rate is likely.

Contribution of the vagal system to changes in small intestine motility in response to restraint stress: an experimental study in dogs

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This paper reports the alterations in small intestine motility in response to restraint stress during fasting and after eating, and the contribution of the vagal system to the pathophysiology of these changes.

Forty dogs were used for the experiments. Small intestine motility was recorded using electromyography (monopolar electrodes) and manometry (submucosal microballoons). Twenty animals received bilateral truncal vagotomy.

Stress led to a significant increase in the rate of intestinal motility (percentage of slow waves followed by action potentials in 1 min), both during fasting (P < 0.001) and after meals (P < 0.001), and also complete abolition of the normal fasting pattern. In dogs undergoing vagotomy, the application of restraint stress led to an increase in the motility rate during fasting (P < 0.001) and a decrease after meals (P < 0.01).

In conclusion, restraint stress induces an increase in small intestine motility, both during fasting and after eating, and the vagal system is partially involved in this hypermotility response to stress.

Effect of blood transfusions on experimental intestinal anastomoses

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It is recognized that blood transfusions alter the immune system. We investigated the effect of blood transfusions on the healing of intestinal anastomoses.

Sixty Lewis rats underwent a 1-cm resection of both the ileum and colon, followed by the construction of an inverted one-layer anastomosis, and subsequently received either 3 ml of saline (control group), 3 ml of Lewis blood (syngeneic group), or 3 ml of Brown Norway blood (allogeneic group) intravenously. The animals were killed 3 or 7 days after the operation and the bursting pressures and collagen levels (hydroxyproline content) of the anastomoses were measured.

The mean(s.d.) bursting pressures of the ileal anastomoses in the three groups were 79(13), 46(14) and 21(12) mmHg on day 3 (P = 0.0001) and 303(50), 254(47) and 198(56) on day 7 (P = 0.001), respectively. The bursting pressures of the colonic anastomoses were 97(19), 66(9) and 47(12) on day 3 (P = 0.0001), and 241(17), 191(35)

and 183(28) on day 7 (P = 0.001), respectively. The hydroxyproline content of the third day anastomoses in the three groups was 90(12), 80(19) and 79(29) µg/5 mm in ileum, and 176(27), 122(30) and 121(27) µg/5 mm in colon (P = 0.003), respectively.

Anastomotic abscesses and generalized peritonitis were not found in the control group. Blood transfusions, particularly allogeneic, significantly increased the incidence of these septic complications. Abscesses around ileal anastomoses were observed in 87 per cent and 60 per cent of the Brown Norway group, 3 and 7 days after operation, respectively (P = 0.0001 and P = 0.005 versus control). This phenomenon was also seen around colonic anastomoses.

We conclude that blood transfusions impair the healing of intestinal anastomoses and increase susceptibility to postoperative septic complications in this experimental model.

Beta galactosidase as a marker of mesenteric ischaemia

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Beta galactosidases are located in high concentration in the brush border membrane of enterocytes. In rabbits, as in humans, there are several existing isoenzymes; for example neutral β-galactosidase which is fixed at the glycocalyx of the enterocytes and another isoenzyme originating in the cytoplasm.

The aim of this study was to find better laboratory parameters for mesenteric ischaemia, and with this objective serum activities of β-galactosidase were investigated. Experimental mesenteric ischaemia in rabbits (n = 30) was induced by clamping the superior mesenteric artery for 90 min. This period of occlusion was followed by 30 min of reperfusion. Blood samples were taken from the ear artery and portal vein before clamping the vessels, 10 min before releasing the clamps, shortly after releasing the clamps and then every 10 min during reperfusion.

Spectrophotometric analyses were performed using the appropriate synthetic substrate p-nitrophenyl-β-D-galactopyranoside. Beta galactosidase was detected after 80 min of clamping the superior mesenteric artery. During the entire period of reperfusion, significant (P = 0.01) increases in serum activity were found. It is notable that other parameters (lactate, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactate dehydrogenase, alkaline phosphatase, serum phosphate) were not altered remarkably during the time of measurement. This suggests that β-galactosidase indicates intestinal ischaemic damage much earlier than other biochemical parameters.

Intravenous aprotinin protects against cell loss during reperfusion of ischaemic small intestine

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The present study aimed to delineate the role of proteases in the pathogenesis of reperfusion damage in an experimental model in the cat. The influence of intraluminal proteases was evaluated by intraluminal aprotinin – a protease inhibitor and stabilizer of proteoglycan polymers – and/or by intraluminal washout, whereas intracellular and serum proteases were inhibited by intravenous aprotinin. In four groups of cats the whole small intestine was isolated on its vascular pedicle. The superior mesenteric artery was occluded for 1 h, then reperfused for another 2 h. At reperfusion the cats were subjected to: no treatment (control, group 1); intraluminal washout with 1 litre physiological solution at 37°C (group 2); washout with the same solution containing aprotinin 1 × 10⁶ units (group 3); intravenous aprotinin 30 000 units kg⁻¹ before occlusion and at 1 h intervals (group 4). Several mucosal enzymatic activities were determined, as well as histological changes. Results are expressed as a percentage of the pre-reperfusion activity in units g⁻¹ muscle protein.

	Reperfusion (h)	Control	Group 2	Group 3	Group 4
n		14	3	3	5
Lactate	1	55.0(4.6)	34.7(9.7)	28.7(2.3)*	78.8(7.4)*
dehydrogenase	2	45.8(4.3)	30.1(10.2)	20.7(3.4)*	62.8(6.3)*
Maltase	1	32.2(3.7)	26.0(5.4)	10.3(0.7)*	49.9(5.2)*
	2	21.5(2.6)	16.8(3.3)	4.0(0.9)*	32.0(3.7)*

Values are mean(s.e.m.). *P < 0.05 versus control group for same duration of reperfusion

The other enzymatic activities (aldolase B and glutamate dehydrogenase) gave similar results. Microscopic analysis showed significantly better mucosal preservation in group 4 only. We conclude that intraluminal protease elimination has no effect on reperfusion damage. The mechanical effect of the washout procedure seems to promote epithelial cell shedding and intravenous aprotinin diminishes mucosal cell loss, the major phenomenon of reperfusion.

Acute mesenteric ischaemia: the second-look procedure with delayed anastomosis without a stoma

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Mesenteric infarction remains a difficult therapeutic problem with an overall mortality rate that exceeds 70 per cent. A surgical approach on two occasions might improve the overall outcome. At the first operation, a vascular surgical approach to the superior mesenteric artery (SMA) was performed followed by bowel resection always without anastomosis. The extremities of the bowel were closed with a stapler. A second-look laparotomy was planned 48 h later to perform the anastomosis.

Seven cases of mesenteric infarction documented by angiography were treated with this protocol over the past 4 years. There were four men and three women. Their median age was 71 (range 56–83) years. The aetiology of the acute mesenteric ischaemia was, in four cases, an embolus of the SMA, in two cases, thrombosis of the SMA, and in one case, Takayashu digestive disease. At the first laparotomy six patients underwent a superior mesenteric embolectomy, with an aortomesenteric graft in one case; the arterial exploration was negative in one further case. All cases required bowel resection. At the second-look laparotomy, one patient had total ischaemia of the bowel and a further segmental resection was needed in three other cases.

Three patients died, two from early recurrence of mesenteric infarction proven by the second-look procedure (day 2) or by a laparotomy (day 7) and one from myocardial infarction 5 weeks after the first operation. A second laparotomy was necessary at day 15 for the patient with Takayashu disease for recurrent small bowel ischaemia which required a resection and anastomosis. The ileocaecal junction was conserved in three of four patients who survived. These

therapeutic methods seem useful for many reasons: the intraoperative assessment of bowel viability is difficult at the first laparotomy. Early planned second-look procedure encourages preservation of maximal bowel length and the ileocaecal junction which is important for intestinal adaptation of short bowel syndrome.

Selective perfusion of vasodilators through the SMA with early second-look laparotomy (after 12–24 h) might improve these initial results.

Tumours of the small bowel: report of 35 cases

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A retrospective clinical review of the past 7 years' experience with small bowel tumours was conducted. In 26 of the 35 cases (74 per cent) the tumours were malignant.

The mean(s.d.) age was 61(18) years for patients with benign and 65(15) years for patients with malignant tumours (*P* not significant). There were 26 men (74 per cent) and nine women. The clinical symptoms were obstruction of the bowel in 12 cases (34 per cent), anaemia and/or haemorrhage in seven cases (20 per cent) and abdominal mass in four cases (11 per cent); in two patients the findings were incidental on laparotomy for rectal cancer and gastric cancer. The other ten patients had symptomatic tumours diagnosed by technetium-99m scan, endoscopy or laparotomy. Resection was possible in 91 per cent of cases (32 patients); in two cases biopsy alone for local extension was performed and in one case (duodenal leiomyoma) duodenal macrobiopsy was performed with a follow-up of 6 years. Benign tumour localization was as follows: two in the duodenum, three in the jejunum and four in the ileum (six leiomyomas, one hamartoma and two fibromas). Malignant tumour localization was as follows: six in the duodenum, seven in the jejunum and 13 in the ileum (seven leiomyosarcomas, nine lymphomas, seven adenocarcinomas and three carcinoids). In 25 per cent of patients there were complications (mostly infections, *n* = 6) in the postoperative period. The mortality rate was 6 per cent (two patients).

In conclusion, this survey demonstrates a predominance of malignant tumours in the small bowel with the majority in the ileum.

Virilizing adrenal ganglioneuroma containing Leydig cells

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An adrenal medullary ganglioneuroma containing Leydig cells and presenting with a virilizing syndrome in a 56-year-old woman is presented. The syndrome, uncommon among adrenal tumours, is associated with masculinization, an elevated serum testosterone level (total testosterone 21 nmol l^{-1} , free testosterone 111 pmol l^{-1}), and normal urinary 17-ketosteroids ($25 \mu\text{mol per 24 h}$). The tumour was localized by computed tomography (CT) and treated by right adrenalectomy. Microscopic examination showed typical features of an adrenal medullary ganglioneuroma, containing Leydig cells with Reinke's crystalloids. Positive immunohistochemical studies enabled their identification and confirmed the testosterone-secreting nature of the Leydig cells. The presence of Leydig cells in the adrenal gland is discussed in the light of embryogenic studies. These show the common origin of the gonad and the adrenal cortex from the coelomic epithelium, the vicinity of the adrenocortical gland and gonad during embryogenesis, the thecal metaplasia of mesenchymal cells, and the development of Leydig cells from Schwann cells.

This is the fourth similar reported case.

Urodynamics in patients with pheochromocytoma: a perioperative study of ten cases

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Alpha-receptors have been demonstrated in the bladder neck, and urinary retention may occasionally be the presenting symptom in pheochromocytoma. This prompted a study of urodynamic profiles in patients with pheochromocytoma.

Ten patients were studied (nine men, one woman). Each had a pheochromocytoma secreting exclusively either noradrenaline (NA) in three cases or adrenaline (A) in two cases, and a blend of NA and A in three cases, and of NA and A and dopamine in two cases.

Urodynamic studies (uroflowmetry, cystometry, profilometry, response to α -adrenolytic agents) were performed with a Urolyn 5000 (Dantec) equipment and external strain gauge transducers. Profilometry was done according to the Brown and Wickham technique. Normal values were those of the International Continence Society. The α -adrenolytic test was done by intravenous injection of moxysilite chloride (0.5 mg kg^{-1}), and was considered positive if urethral pressure dropped by 30 per cent after 10 min.

Ten patients had a preoperative study, omitting the α -adrenergic test in two; five consented to a postoperative study. Before operation an increased urethral pressure was found in seven of ten patients regardless of the response pattern, and a response to α -adrenolytic agent in seven of eight patients. After operation there was good correlation between a positive preoperative α -adrenolytic response and a decrease in urethral pressure in four of five patients.

In conclusion, urodynamics in patients with pheochromocytoma shows a typical α -adrenergic pattern and might explain bladder dysfunction as a presenting symptom.

Hyperthyroidism and concurrent thyroid carcinoma

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The incidence of thyroid carcinoma in patients having surgical treatment for hyperthyroidism was evaluated. During the period 1986–1991, 138 thyroidectomies were performed for hyperthyroidism in this department and thyroid carcinoma was found in eight cases (5.8 per cent). Eighty of 138 cases were multinodular toxic goitres, 33 were toxic diffuse goitres, 25 were toxic adenomas: distribution of

carcinoma among the groups was four, two and two cases respectively. During the same period of time 958 other thyroidectomies were performed and carcinoma was diagnosed in 66 cases (6.9 per cent).

There were seven women and one man with thyroid carcinoma and coexisting hyperthyroidism. The mean (range) age was 43 (19–65) years. All patients had received preoperative treatment with propylthiouracyl or methimazole. Bilateral subtotal thyroidectomy was performed in six cases, near-total thyroidectomy in one case and total thyroidectomy in one. Papillary carcinoma accounted for 88 per cent of cases (seven of eight) and follicular carcinoma for 12 per cent (one of eight). Three cases of papillary carcinoma were occult carcinoma with diameter < 1 cm. Three cases received 100 mCi iodine-131 after operation.

There was no morbidity. The median (range) follow-up period was 30 (10–45) months. There was no recurrence in this period.

In conclusion, the possibility of thyroid carcinoma must be considered in surgical treatment of hyperthyroidism.

Evolution of Graves' ophthalmopathy after subtotal thyroidectomy and radioactive iodine therapy

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The place of subtotal thyroidectomy in the treatment of Graves' ophthalmopathy is controversial. Views about the use of radioactive iodine therapy for hyperthyroidism seem to conflict even more.

A prospective study is presented on 30 patients (60 orbits) who presented with Graves' ophthalmopathy. Fifteen had subtotal thyroidectomy (group I, 30 orbits, three men and 12 women, age range 18–45 years) and 15 had radioactive iodine therapy (group II, 30 orbits, four men and 11 women, age range 25–62 years). All patients included in the study were scanned in both axial and coronal planes. Computed tomography was used to analyse optic nerve, lacrimal gland, bony orbit, proptosis and extraocular muscles (superior muscle group and inferior rectus in coronal planes, and lateral and medial rectus in axial planes).

Improvements were noticed in group I 12 months after treatment, with significant differences in the following parameters: reduction of the extraocular muscles (medial rectus ($P < 0.01$), superior muscle group ($P < 0.01$), lateral rectus ($P < 0.01$), and inferior rectus ($P < 0.01$)) and reduction of proptosis ($P < 0.01$). There were no significant changes in group II in spite of some cases of extraocular muscle and proptosis reduction.

Subtotal thyroidectomy seems to improve the ophthalmopathy of Graves' disease more than radioactive iodine therapy.

Surgical correction of exophthalmus

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Surgical methods which have been used for the correction of exophthalmus either cannot be applied to severe cases or present long-term sequelae. A modification of a technique already reported by Tessier (1969) was therefore developed. It consists of an osteotomy of the supraorbital and lateral orbital rim, removal of the lateral orbital wall, interposition of calvarial bone grafts between skull and osteotomized rim and occasional lipectomy.

Seven patients (five women and two men) underwent surgery for severe exophthalmus due to Graves' disease ($n = 4$) or meningioma ($n = 3$) with a follow-up ranging from 6 months to 4 years. The exophthalmus was corrected in all cases and the coexisting diplopia in five. No postoperative complications or major long-term sequelae were observed.

It is concluded that this method offers considerable advantages in increasing the orbital capacity, permitting the eyelids to close over the eyeball and improving the aesthetic appearance without adverse sequelae. It appears to be superior to previously reported techniques.

Total thyroid resection as an adequate surgical therapy for Graves' disease

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The thyroid cell is the target of the autoimmune process in Graves' disease. Subtotal resection is the usual treatment when surgical therapy is demanded. Remnant thyroid tissue is nevertheless capable of stimulating the immune process, which leads to recurrent hyperthyroidism and goitre in about 10 per cent of patients.

Forty-five patients underwent total thyroid resection for Graves' disease at our institution. The clinical outcome has been investigated 10–36 months after the operation in 40 cases. A low complication rate (hypothyroidism, $n = 1$; recurrent nerve palsy, $n = 1$) and the wide acceptance of lifelong medication with thyroxine support the use of this method of treatment in order to avoid a relapse.

Highly invasive recurrence of thyroid cancer: opportunity for radical surgery

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Although differentiated thyroid cancer has a good prognosis, a certain percentage of patients present, years after the first surgical excision, with highly invasive local recurrence. This is responsible for death more often than are distant metastases.

In view of the slow evolution of this type of cancer we prefer a combined ablative and reconstructive operation. This also applies when there is an invasion of the musculocutaneous structures. Of 258 patients affected by differentiated thyroid carcinoma over a 4-year period (October 1987 to November 1991), five were referred to us because of a local recurrence after having received a near-total thyroidectomy. The mean age was 63.2 years and mean follow-up was 2.8 years. In spite of suppressive and radioiodine therapy in all patients, a local recurrence appeared a mean of 7.6 years after the initial surgical treatment. All patients underwent 'block resection' of the recurrent tumour, including skin, subcutaneous tissue and invaded strap muscles up to the pharyngotracheal plane. The residual defect (the largest was 9×5 cm) was repaired by a pectoralis myocutaneous flap. Postoperative histological examination confirmed in all cases the complete excision of the tumour. One patient died 14 months after the operation from pneumonic metastases, whereas all the others are enjoying good health. Their long-term survival suggests that radical extirpation of the recurrent lesions of thyroid carcinoma should always be attempted.

Importance of ultrasonography after thyroid resection: a prospective trial with 100 patients

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Whereas ultrasonography (US) of the thyroid is widely accepted for the preoperative evaluation of a goitre, its role in postoperative follow-up has yet to be established.

One hundred patients admitted to our institution for surgery of benign thyroid disease were followed up with US 2, 90 and 180 days after surgery. At day 2 it was not possible to distinguish the thyroid remnant from haematoma. In contrast, 3 and 6 months after operation the remnant size was measured precisely, providing a reliable indicator of relapsing goitre ($n = 4$). The evaluation of US was a difficult task, especially after resection of nodules. The combination of the thyrotropin-releasing hormone test and US made thyroid scintigraphy superfluous in patient follow-up.

Thyroid surgery in patients aged over 80 years

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In the past 5 years (1987–1991), 12 patients over 80 years of age (mean 81.4 years) have been submitted to surgical treatment for

thyroid pathology. The findings were five carcinomas (three papillary and two anaplastic) and seven nodular goitres. In six of these last cases the main indication for surgical treatment was severe dyspnoea due to tracheal compression. In the remaining case thyroidectomy was performed because of a false cytological diagnosis of malignancy. Dyspnoea, which in two cases was accompanied by marked oedema in the upper part of the chest, represented an absolute surgical indication in all six cases because of the gross compromise of respiratory function. One of the patients required intubation and mechanical ventilation and subsequent urgent surgical treatment. None of the patients with carcinoma had respiratory problems. Eleven patients were treated by cervical exploration. One patient required sternotomy because of a huge mediastinal goitre. Four subtotal thyroidectomies and three lobectomies were performed in the patients with goitre and three total thyroidectomies (two with unilateral neck dissection) in the differentiated carcinomas. The two anaplastic carcinomas were treated by palliative surgery. There has been no intraoperative death in the present series, nor any significant surgical complication. Tracheal compression disappeared in all six dyspnoea patients and respiration was improved. The mean survival was 12 months for anaplastic carcinomas. All the patients operated on for differentiated carcinoma are still alive after 5, 10 and 13 months.

We conclude that advanced age is not a contraindication to surgery in patients with thyroid carcinoma and in those with tracheal compression due to goitre.

Systemic AL amyloidosis presenting as an intrathyroid haemorrhage

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Thyroid amyloidosis is frequent but is usually asymptomatic. The case is reported of a painful nodular goitre which revealed an amyloidosis associated with a biclonal gammopathy.

A 77-year-old woman, whose goitre had been found 7 months previously, was admitted in March 1991 with neck pain associated with a moderate hyperthyroidism and an increased erythrocyte sedimentation rate. Clinical examination revealed a goitre with a painful left cervical nodule, dysphonia, anorexia, weight loss of 16 kg over 2 years, and tiredness. The nodule puncture was haemorrhagic, and cytology found no suspect cells. The goitre appeared nodular on ultrasonography, with a 3.3-cm diameter left nodule, and thyroid scanning showed an increased uptake in the lower left part of the gland with a low technetium uptake in the other part of the gland. Laboratory examination revealed a monoclonal proliferation of two light chains, IgG lambda and IgA kappa, and a systemic amyloidosis of AL type with a nephrotic syndrome and a rapidly evolving renal insufficiency. The radiographic bone survey gave normal results. The bone marrow biopsy showed less than 5 per cent dystrophic plasmacytes and amyloid surrounding the blood vessels. The gingival biopsy confirmed amyloidosis. A subtotal thyroidectomy was performed in May 1991: the histological examination revealed a diffuse amyloidosis of AL type, an intranodular haemorrhage, and no sign of thyroiditis.

In this case, an intranodular haemorrhage and moderate hyperthyroidism revealed an amyloid goitre and a diffuse amyloidosis of AL type associated with a biclonal gammopathy. This presentation is atypical: only five cases of subacute thyroiditis-like syndrome associated with a 'secondary' amyloidosis have been described in Japan.

Surgical treatment of hyperparathyroidism after kidney transplantation

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Studies on the surgical treatment of hyperparathyroidism (HPT) persisting after kidney transplantation are scarce. Since June 1984, 15 patients with a kidney graft have been operated on in our unit for HPT (3.3 per cent of the total population of the transplanted patients followed during the same period). They were either symptomatic (bone pain, conjunctivitis, transplant lithiasis) or had increasing serum calcium levels. The operation failed in two patients where fewer than four glands were identified. The remaining 13 patients

underwent three different surgical procedures: total parathyroidectomy with intramuscular parathyroid grafting in two cases, total parathyroidectomy with presternal subcutaneous grafting in six cases and subtotal parathyroidectomy removing two or three glands and leaving in place the grossly normal parathyroids in five cases. At the last check-up, all the patients were normocalcaemic and, except for one woman who is again in mild renal failure, blood parathyroid hormone levels were in the normal range.

We conclude that in patients with a functioning kidney graft presternal subcutaneous grafting of parathyroid tissue is as efficient as intramuscular grafting after total parathyroidectomy, that total parathyroidectomy is not required in every case and that subtotal parathyroidectomy, removing only the grossly abnormal parathyroid glands, may be sufficient.

Initial surgery for primary hyperparathyroidism in France: a multicentre study

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In 1990 the authors were commissioned by the French Association of Surgery (AFC) to summarize the experience of French and foreign members dealing with primary hyperparathyroidism (PHP). Among the 79 AFC surgeons approached, 29 (37 per cent) were trained for parathyroid surgery and performed more than one parathyroid exploration per month.

Before initial surgery 17 per cent of the AFC surgeons dispensed with localization studies. In the case of non-acute PHP 15 per cent preferred to await positive imaging before deciding to operate.

The majority of AFC surgeons (98 per cent) routinely attempted to identify all four glands but the success rate was only 70.2 per cent. Frozen section was used by 83 per cent to confirm the nature of the parathyroid tissue in 51 per cent of cases and to decide on the extent of resection in 33 per cent of cases.

A total of 4830 case records was available for detailed study: 3702 (76.6 per cent) single adenomas; 720 (14.9 per cent) multiglandular lesions; 55 (1.1 per cent) multiple endocrine neoplasias; and 70 (1.5 per cent) cancers.

Among 283 negative neck explorations (5.9 per cent) an adenoma was missed in 78 patients. Diagnosis of PHP was confirmed in 33 further patients who are awaiting surgery. Conversely, hypercalcaemia was shown to be due to another cause in 68 other patients. In the remaining 104 patients who have not undergone reoperation, diagnosis of PHP was not confirmed. Of the 70 patients with cancer only 17 had a recurrence, or metastases, or died of the disease.

The overall mortality rate was 0.6 per cent and the rate of permanent laryngeal paralysis 1.5 per cent.

After initial surgery, 89.3 per cent of patients were cured, 3.4 per cent had definitive hypoparathyroidism and 7.3 per cent had persistent or recurrent hyperparathyroidism.

Intraoperative identification of parathyroid glands with methylene blue infusion

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A retrospective study to evaluate the peroperative staining ability of methylene blue in hyperparathyroidism was carried out. Methylene blue was administered intravenously, over 45–60 min preceding exposure of the parathyroid glands, to all patients undergoing cervical exploration for hyperparathyroidism. The initial dosage was modified over time to 7.5 mg per kg body-weight. Intraoperative staining of parathyroid glands with methylene blue was used in 120 cervical explorations for hyperparathyroidism in 110 patients. The dye clearly stained 66 of 67 adenomas (98.5 per cent) and 194 of 198 hyperplastic glands (98.0 per cent). No recurrences were observed in 66 patients undergoing surgery for an adenoma. Six of 48 patients (12.5 per cent) had recurrences following surgery for hyperplasia of the parathyroid glands.

We found methylene blue to be an effective, safe and easy method for quick identification of abnormal parathyroid glands. Its use shortened operation time considerably.

Cystic parathyroid adenomas: how they differ from solid parathyroid adenomas

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The data for all patients undergoing surgery in our institution between 1 January 1987 and 31 December 1990 for primary hyperparathyroidism (pHPT) excluding parathyroid carcinomas, hyperplasias and reoperations for pHPT were documented prospectively. The data for the patients with cystic parathyroid adenomas according to the definition suggested by de Ridder *et al.*¹ were compared with those of patients with solid parathyroid adenomas with respect to clinical and operative findings.

Six of 126 patients with pHPT were found to have a total of seven cystic adenomas (prevalence 4.8 per cent). The male:female ratio was 1:2 for solid and cystic adenomas. No difference was found with respect to age distribution. Two patients with cystic adenomas presented with a hypercalcaemic crisis. In patients with cystic adenomas, alkaline phosphatase (median 348 units l⁻¹ versus 165 units l⁻¹) and serum parathyroid hormone (multiple of normal value: median 12.4 versus 2.0) levels were higher. Other parameters of calcium metabolism showed no difference. The weight of the removed cystic adenoma was higher than solid adenomas (median 8.5 g versus 1.1 g). Six of seven cystic adenomas were related to the upper parathyroid glands. Four (57 per cent) of them were displaced to the upper posterior mediastinum. Only 3.3 per cent of solid adenomas were found in this location.

In conclusion, cystic adenomas occur more frequently than previously thought and, in contrast to previous reports, are more often found in women. Of patients with pHPT, those with cystic adenomas show a higher parathyroid activity. Cystic adenomas of the parathyroid should be considered as a differential diagnosis of cystic tumours in the upper mediastinum.

1. de Ridder VA, Brom HL, Blok P. Hyperparathyroidism due to primary cystic parathyroid adenoma. *Neth J Surg* 1986; **38**: 134–7.

Ultrasonography after thyroid resection: a prospective trial on 100 patients

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Whereas ultrasonography (US) of the thyroid is widely accepted for the preoperative evaluation of a goitre, its role in postoperative follow-up has to be established.

A total of 100 patients admitted to our institution for surgery of benign thyroid disease was followed up with US at days 2, 90 and 180 after surgery. At day 2, it was not possible to distinguish the remnant thyroid tissue from haematoma. In contrast, at 3 and 6 months after the operation the remnant size could be measured exactly, providing a reliable clue for relapsing goitre ($n = 4$).

The evaluation of US was difficult, especially after resection of nodules. The combination of the thyrotropin-releasing hormone test and US made thyroid scintigraphy superfluous at follow-up.

Mucoepidermoid carcinoma of the thyroid gland: a case report and review of the literature

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A case of primary mucoepidermoid carcinoma of the thyroid gland in a 38-year-old woman is reported.

This is the seventh reported case and the first to be reported in the isthmus. It was found at a routine clinical examination and was a solitary cold nodule without palpable regional lymph nodes in a euthyroid patient.

Initial treatment was isthmus resection, and histological frozen sections were negative for malignancy. Definitive pathological examination showed mucoepidermoid carcinoma. The patient underwent total thyroidectomy with bilateral neck node dissection and radioiodine therapy before hormonal replacement therapy. No lymph node metastases were found.

A rich histological picture is presented: as is well documented in the literature, microscopic findings revealed an abundant fibrous goitre with inclusions of cystic structures surrounded by cylindrical or malpighian cells. In addition, some malpighian cell clusters were encountered containing several psammomatous calcifications but without follicular formations. The extratumoral parenchyma showed lesions of chronic lymphocytic thyroiditis. Tumour cells were positive on immunocytochemical tests for cytokeratin and carcinoembryonic antigen and negative for thyroglobulin and calcitonin.

There is still debate about the histogenesis of this entity and it is not clear whether it develops from ectopic salivary gland tissue or originates in solid cell nests. Finally, prognosis is difficult to define as follow-up data are not available from previously reported cases.

Adrenal tumours

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Adrenal tumours are rare. The diagnosis of non-functional tumours has been made easier by ultrasonography. At this clinic, over the past 15 years, we have treated 39 patients with adrenal tumours, three of which were metastases from a melanoma, a colonic carcinoma and a hepatocarcinoma, respectively. The patients comprised 13 men and 26 women, of mean age 52 (range 19–76) years. Fifteen patients presented with pheochromocytoma syndrome, eight with Cushing's syndrome, two with a virilizing syndrome and one with Conn's syndrome. An incidental diagnosis was made in eight of 13 non-functional tumours. No differences were present as far as the site of tumour, sex and age between functional and non-functional tumours, but the latter were larger. All patients underwent adrenalectomy. Hepatic resection was performed in the patient with hepatocarcinoma, and splenectomy and left nephrectomy were performed in another case when a large tumour was present. There were no postoperative deaths. The tumours secreting sexual hormones were malignant and these patients died 3 and 12 months after adrenalectomy from metastatic disease. Non-functional primary tumours comprised one myelolipoma, three adenomas and six carcinomas, all of the last being >6 cm in diameter. Three patients died 13, 14 and 24 months after adrenalectomy from metastatic disease, while the others are still free of disease. The three patients with metastatic adrenal tumours died 8, 35 and 47 months after adrenalectomy. This study confirms the importance of early ultrasonographic detection of adrenal tumours and stresses the high incidence of malignant lesions if the tumours are sizeable or secreting hormones.

Value of intraoperative tumour staging for surgical management of papillary carcinoma of the thyroid

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Radical surgery in the management of papillary carcinoma of the thyroid is still controversial. This study aimed to analyse the value of intraoperative tumour staging in definitive decision making at operative procedures.

Between 1955 and 1989, 195 patients were treated for papillary carcinoma of the thyroid (histopathology: pT₁₋₃, 92 per cent; pT₄, 8 per cent; lymph node metastases, 32 per cent). Of these, 174 had a total thyroidectomy and in 13 cases a lobectomy and contralateral subtotal resection was performed. Eight patients had a palliative debulking. Postoperative radioactive iodine therapy was given in 92 per cent of cases.

The tumour stage was correctly estimated during surgery in 121 cases (62 per cent). An understaging in 69 cases (36 of which were occult carcinoma) led to a subsequent total thyroidectomy. The rate of error in the clinical estimation of lymph node metastases was 5 per cent (seven false negative, three false positive). Following a median follow-up of 10 years, 49 patients had tumour recurrences (19 local recurrences, 17 lymph node and 13 distant metastases). The overall mortality rate was 4 per cent. There was no significant correlation between the frequency of recurrence and the intraoperative understaging.

The intraoperative tumour staging is an effective tool for decision making and stage-dependent surgical management of papillary carcinoma of the thyroid. The surprising high rate of miscalculation of the primary tumour stage was due to the number of cases of occult carcinoma. We do not recommend a secondary thyroidectomy in occult carcinoma or in a carcinoma <1.5 cm in diameter.

Acute upper gastrointestinal bleeding: effects of intravenous omeprazole on intragastric pH and serum pepsinogen I and gastrointestinal hormones

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This study was designed to identify the modifications in 24-h intragastric pH and serum pepsinogen, gastrin, VIP, bombesin and somatostatin levels in patients with acute upper gastrointestinal bleeding (AUGB) treated with intravenous omeprazole.

Sixteen patients (14 men, two women) of mean (s.d.) age 53 (18) years were admitted as emergencies with AUGB confirmed by endoscopy. All patients received an intravenous bolus injection of 80 mg omeprazole followed by injection of 40 mg of the drug every 8 h. Serum concentrations of pepsinogen, gastrin, VIP, bombesin and somatostatin were measured before treatment and at 3, 24 and 48 h by radioimmunoassay. Intragastric pH was recorded continuously 1 h before the treatment (basal) and continued for 24 h. Statistical analysis was by the Wilcoxon signed rank test.

Pepsinogen increased ($P < 0.01$) from a mean (s.d.) basal value of 102 (73) $\mu\text{g l}^{-1}$ to 340 (228) $\mu\text{g l}^{-1}$ at 48 h. Basal gastrin was 43 (17) ng l^{-1} and increased to 68 (41) ng l^{-1} at 48 h. In contrast, bombesin decreased from a basal value of 53 (22) pg ml^{-1} to 37 (11) pg ml^{-1} ($P < 0.05$) at 48 h. There were no significant changes in serum levels of VIP and somatostatin after omeprazole. Basal intragastric pH value was 1.3, increasing to ≥ 4.0 31 (15) min after the initial dose of omeprazole. The pH remained above 4.0 during >90 per cent of the recording time. The clinical evolution was satisfactory in all patients.

This study shows that in patients with AUGB, intravenous omeprazole causes an early and consistent increase in intragastric pH which may contribute to changes in the level of serum pepsinogen and digestive hormones.

Benign gastric tumours: a report of 58 cases

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A study of 58 patients with benign gastric tumours who underwent surgical treatment in the past 35 years is presented. Gastric polyps, both adenomatous and hyperplastic (36 cases) were the most common. Next in frequency were mesenchymal tumours (11 cases): seven neurilemmoma, one leiomyoma, one fibroma, one lipoma, one myxoma and heterotopic pancreas (11 cases). Nine cases with adenomatous polyps underwent malignant change, which was more frequent in those of large size and those situated farthest from the pylorus.

Recurrence including lymph node metastases was identified in only one instance. In tumours of mesodermal origin and aberrant pancreas, malignant transformation, recurrences or metastases did not develop after operation. Clinical signs and symptoms were not specific, six cases were symptomless; haemorrhage occurred in 32 per cent of our series. Improved radiological technique and the use of endoscopy offered an increasing chance of diagnosis. Biopsy through the fiberoptic gastroscope can identify protuberant tumours with acceptable accuracy. The definitive diagnosis was established when the whole resected specimen was examined histologically. A real or theoretical risk of malignant transformation exists for all these growths. This fact, together with some uncertainties of pathological examination led us to prefer, especially for antral localizations, segmental gastrectomy instead of local excision (polypectomy with a margin of surrounding gastric mucosa or wall).

Ruptured left gastric artery aneurysm

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Arterial aneurysms of the digestive tract are relatively rare, left gastric artery aneurysms representing less than 2 per cent of cases. A case is presented for which we describe the history and diagnosis by means of angioscanner, position of the aneurysm and its treatment.

An 82-year-old man with a significant previous vascular history, including two femoral aneurysms and one subrenal abdominal aneurysm which underwent operation in 1985, at which time the arteries of the digestive tract were normal on angiography, presented in December 1990 with a marked haematemesis. Endoscopy proved difficult because of the presence of numerous clots. An aortic gastric fistula was suspected. Contrast-enhanced computed tomography was performed. This showed a large retrogastric mass which was partially opacified and was found to be in contact with the stomach. At the point of contact there was loss of gastric substance. A diagnosis of an intragastric rupture of a left gastric artery aneurysm was suspected. At surgery, a partially thrombosed aneurysm in communication with the lesser curve of the stomach was found. A partial longitudinal gastrectomy was performed, which included the lesser curve. The artery involved was ligated at its origin and an aneurysm measuring 8 cm in diameter was resected. No other abnormality was found. There were no postoperative complications. Culture of the aneurysm was sterile. Histology showed evidence of thrombosis and calcification. The aetiology was due to atheroma with a possible dysplastic element.

Left gastric artery aneurysm is a very rare finding. It most frequently presents with rupture resulting in a haemoperitoneum or haematemesis. Arteriography is the definitive means of diagnosis. The condition is generally treated by gastrectomy.

This case clearly demonstrates the computed tomographic characteristics of this lesion. In view of the specific localization of the lesion, conservative resection was possible.

Gastroplasty for morbid obesity

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Morbid obesity is always due to an excess of food intake and its treatment logically implies the restriction of food; unfortunately, dieting alone fails in 95–100 per cent of cases and a surgical

alternative has been proposed. This report describes the results of 500 silicone ring vertical gastroplasties accomplished during the past 8 years. Operative morbidity, which is decreasing with increased surgical experience, includes wound infection, subphrenic abscess, gastric perforation, skin dehiscence and incisional hernia.

Long-term complications have been observed, most of them related to dietary errors; these include oesophagitis, outlet stricture and staple-line dehiscence.

When carefully selected and adequately counselled by a team of physicians, surgeons, psychiatrists and dieticians, patients who have undergone this surgery will lose one-third of their weight without particular difficulty and maintain their new weight (to their great satisfaction); after 1 year, over 70 per cent of patients have a body mass index of <30. Loss of weight that was too slow, or weight gain, were usually the results of dietary errors (excessive consumption of sugared drinks, chocolate, alcohol, etc.). This finding shows the necessity of close follow-up following surgery. Bearing that in mind, we nevertheless consider that silicone ring vertical gastroplasty is the best therapy available for morbid obesity.

Vertical banded gastroplasty versus adjustable silicone gastric banding in the treatment of morbid obesity: a preliminary report

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Having performed vertical banded gastroplasty (VBG) for the treatment of morbid obesity for the past 9 years, adjustable silicone gastric banding (ASGB) was introduced in our institution in September 1991. The results of VBG have been good with regard to weight loss and complication rate. Nevertheless, VBG produces a definitive organic modification of the stomach. This operation is not reversible and reoperation after VBG is generally difficult. ASGB may cause less damage to the stomach. The stoma size is adjustable on an outpatient basis.

A prospective clinical trial is reported, in which the weight loss following ASGB and VBG is compared.

Antral patch pyloroplasty: a new method for treating obstructing pyloric ulcer

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Pyloric stenosis due to benign ulcer is a serious disease for which several surgical procedures have been used, all of which, however, have drawbacks. A new experimental method was therefore tested in the dog in an attempt to circumvent these disadvantages.

In the test series laparotomy was performed in seven beagles to produce an obstructing pyloric ulcer model by means of a 1-ml injection of a 0.5 per cent glutaraldehyde solution into the anterior portion of the pyloric wall. Antral patch pyloroplasty (APP), consisting of an inlay in the longitudinally excised pyloric ulcer area of a vascularized 3 × 4 cm oval patch of antral gastric wall, was performed 3 weeks later. Gastric emptying, measured by a γ camera, was investigated with liquids and solid foods before and after ulcer production and at 6 and 24 weeks after APP. Histological examination was also used to assess the ingrowth of the patch graft.

In all dogs the antral inlay remained well vascularized and showed perfect ingrowth in the pyloric canal. Gastric emptying, considerably delayed after glutaraldehyde-induced ulcer production, for both solid and liquid food, showed complete recovery within 6 months of APP. Histological examination showed ingrowth of all layers of the patch into the pyloric wall, including the important muscular layers responsible for normal gastropyloric outlet control.

APP proved to be a safe and reliable form of widening the stenosed pyloric channel. Complete ingrowth of the antrum in the pylorus ensures a permanent normal physiological gastric outlet mechanism.

Remedial operations for postgastrectomy syndromes

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From January 1986 to September 1990, 24 patients have undergone 28 remedial operations for postgastrectomy syndromes without any mortality. Of these, the indication for surgery in the majority was alkaline reflux gastritis in 75 per cent (18 of 24). Even though the clinical presentation of most of these patients with abdominal pain (83 per cent) and bile vomiting (58 per cent) is confusing, careful history, complete gastrointestinal examination, gastroscopy and histopathological evaluation, with an adequate period of conservative therapy, aided classification into one of the well defined clinical patterns. The initial operations mostly causing postgastrectomy syndromes were Billroth II resection (46 per cent) and vagotomy plus gastrojejunostomy (37 per cent). Roux-en-Y (RY) diverting anastomosis was the operation of choice (87 per cent) in our practice. Four patients (17 per cent) had a second remedial operation for the relief of symptoms; a Henley operation changed to RY and a RY changed to a hemigastrectomy and RY for alkaline reflux gastritis, a Brown anastomosis altered to RY for afferent loop syndrome, and a RY reconstructed with high gastric resection for Roux stasis syndrome. After 1–5 years of follow-up, overall results showed that 83 per cent of patients were Visick grades 1 and 2. The failure rate was 17 per cent. Thus, it is important to determine the type of remedial operation to return the patient to a normal lifestyle. Although 24-h pH monitoring, radionuclide studies and enterogastric bile reflux measurements play a significant role in the management of postgastrectomy syndromes, we had similar results as in the literature without the use of these procedures.

Disturbed oesophageal motility after gastrectomy

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The aim of this study was to examine the motility of the oesophagus after gastrectomy and to explain the patients' symptoms.

Oesophageal manometry with a catheter microtransducer was performed as a functional diagnostic method on 30 patients after gastrectomy because of gastric cancer (18 men, 12 women; mean age 64 years). Subsequently their symptoms were recorded. Of the patients 21 (70 per cent) complained of reflux discomfort and symptoms of disturbed peristalsis (dysphagia, odynophagia). A loss of weight ranging from 5 to 17 kg occurred in 40 per cent of the patients. A total of 29 patients (97 per cent) showed pathological patterns of contraction (repetitive, simultaneous, deformed contractions) especially in the distal part of the oesophagus. The contractile force was decreased on average by 10 mmHg in that area. The resting pressure of the upper sphincter was also reduced by about 10 mmHg.

These results can be explained by an increased postoperative reflux (absence of the lower sphincter) and the changed biomechanics of the oesophagus (decreased longitudinal tension, postoperative adhesions) caused by the operation.

The results of this study demonstrate the use of postoperative manometry in patients who have undergone gastrectomy to explain their symptoms. This technique is most useful in the detection of oesophageal motility disturbances in these patients.

Primary gastric lymphoma: prognosis and treatment

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Primary gastric lymphoma is a relatively rare tumour that constitutes 2–5 per cent of malignant tumours of the stomach. It has a better prognosis than gastric carcinoma. Surgery is the treatment of choice although the role of radiation therapy and chemotherapy is still to be elucidated in the absence of standard guidelines.

This study reviews 38 patients who underwent surgery for primary gastric lymphoma from January 1980 to December 1990. The mean age was 57 (range 22–86) years. Mean follow-up was 37 (range 6–108) months. Patients were classified according to the systems of Ann Arbor and the Working Formulation for non-Hodgkin's Lymphoma. The probability of survival was calculated by the Kaplan–Meier method, and survival curves were compared using the log rank test.

The commonest symptom was epigastric pain (87 per cent). Eight patients presented acutely, seven with upper gastrointestinal bleeding and one with a gastric perforation. Endoscopy was the most useful method for diagnosis, although only 50 per cent of the patients had biopsy specimens positive for lymphoma and biopsies were negative for tumour in 26 per cent of the patients. Ten patients underwent total gastrectomy, 27 had a partial gastrectomy and there was one local excision. The operative mortality rate was 8 per cent (three patients) and the morbidity rate 32 per cent. According to the Ann Arbor system 71 per cent of the patients were classified as stage Ie and 29 per cent as stage IIe. According to the Working Formulation 42 per cent of the patients had low grade lymphoma, 11 per cent had lymphoma of intermediate grade and 47 per cent had high grade tumours. Survival rate at 72 months was 73 per cent. Factors significantly influencing survival were histological grade ($P < 0.001$), tumour penetration ($P < 0.003$) and size ($P < 0.046$).

We conclude that endoscopy is the best diagnostic method despite its low sensitivity. According to our experience, surgery is the treatment of choice for stages I and II, and should be as conservative as possible. Histological grade, tumour penetration and size are factors that significantly influence survival.

Changing epidemiology of gastric cancer

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Gastric cancer is generally perceived to be a disease in decline because of the worldwide fall in mortality rates, which has been most marked in the USA. The surgical workload of this hospital, however, has not declined and therefore the hypothesis that the decline in mortality over the past 30 years might be due to improved surgical technique was explored. Local audit figures demonstrate that over the past 12 years the number of operations for gastric cancer in Edinburgh hospitals has not declined. Similarly, for Scotland the incidence of gastric cancer recorded by the national cancer registration scheme showed no decline and standardization of the data showed a marginal decline for men only, while the decline for women was not significant. Standardized mortality, on the other hand, fell significantly for both sexes. A review of operative mortality in English language publications from 1970 revealed 207 papers, of which 103 were considered suitable for inclusion. Operative mortality fell significantly over this period, the mean(s.e.m.) operative mortality rate in series closing before 1970 being 16.2(2.2) per cent (95 per cent confidence interval 11.6–20.8), while in series closing before 1990 the mean(s.e.m.) operative mortality rate was 7.8(1.0) (95 per cent confidence interval 5.8–9.9). Only one series failed to show a significant decline. A review of survival after curative or radical resection for gastric cancer in 101 English language publications since 1920 showed that the 5-year survival rate rose from 38 per cent in series closing before 1970 to 55 per cent in series closing before 1990. This increase is not confined to Japanese series. We conclude that the disparity we have demonstrated in Scotland between marginally declining incidence rates and significantly declining mortality rate is due in part to improved surgical technique.

Carcinoma of the stomach

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This study examines the survival rate of 70 patients with gastric cancer treated consecutively by two endoscopist surgeons in one district general hospital over a 5-year period.

Surgical and pathological data have been collected retrospectively from the patients' notes. Follow-up of patients was by reference either to case notes, the general practitioner or to the Cancer Registry.

Of 1200 patients presenting for upper gastrointestinal endoscopy, 70 were found to have gastric cancer. There were 42 men and 28 women with a median age of 73 (range 38–91) years.

Only three patients were found to have early carcinoma limited to the mucosa. All other patients had either lymph node spread (60 per cent of patients) or distant metastases. Just under half the patients had laparotomy alone or were inoperable. Median survival for the whole group was 4 months (range 5 days to 30 months). Few patients received any medical or nursing counselling.

The results reveal that the majority of surgery was of palliative value only. There is a requirement for the psychological needs of patients to be evaluated and for the appropriate terminal care to be provided.

Early and long-term results of total gastrectomy for carcinoma of the gastric stump

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From 1973 to 1991, 24 patients presented with adenocarcinoma of the gastric stump. There were three women and 21 men, mean age 64 (range 46–75) years. Twenty-one Finsterer, two Pólya gastrectomies and one gastroenteroanastomosis had been performed. Indications were gastroduodenal ulcer (22), gastric polyp (one) and gun injury (one). Adenocarcinoma was diagnosed at a mean (range) of 30 (10–45) years after the initial procedure. The diagnosis was made following weight loss (six), epigastric pain (ten), upper gastrointestinal bleeding (four) and gastrocolic fistula (one). Three tumours were revealed by routine endoscopy. Twenty-one patients had total

gastrectomy (extended to spleen and pancreas for 14). One hepatic and two colonic resections were also undertaken. Twenty-one tumours were located at (17) or just above (four) the gastrointestinal anastomosis and two were fundal. Mean tumour diameter was 4.7 (range 0.6–10) cm. Three tumours were not resectable. The gastric lesions were classified as T₁N₀M₀ (one), T₂N₀M₀ (six), T₃N₀M₀ (six), T₄N₀M₀ (two). Six patients had metastatic extension with five T₃N₊M₀ and one T₄N₊M₊ tumours. Ten of the 21 tumours were poorly differentiated carcinomas. There was one postoperative death (5 per cent). Complications included subphrenic (three) or parietal abscess (one), wound dehiscence (two), fistula (three) and myocardial infarction (one). Actuarial survival rate after resection is 68.4 per cent at 1 year, 50.9 per cent at 5 years and 40.7 per cent at 10 years. The three patients with no resection died 3 months after laparotomy. Cancer of the gastric stump has been seen especially following Billroth II procedure.

Regular fibroscopic screening commencing 10 years after the operation should ensure early diagnosis of tumours.

Surgical treatment with 88 per cent resectability compares favourably with results from other studies, while the postoperative mortality rate remains acceptably low.

Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970

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The aim was to ascertain whether there has been improvement in 5-year survival rates following surgery for gastric cancer and, if so, whether these improved results have contributed to the observed decline in mortality rate. All English language publications from 1970 on the surgical management of gastric cancer were reviewed. While the proportion of patients coming to operation has fallen from 92 per cent before 1970 to 71 per cent before 1990, the proportion of patients operated on and coming to resection has increased from 37 per cent before 1970 to 48 per cent before 1990. This suggests improved preoperative staging leading in turn to better patient selection for operation. The 5-year survival rate following all resections has increased from 21 per cent before 1970 to 28 per cent before 1990, while that following curative or radical resection has increased from 37 per cent to 55 per cent over the same period. It is likely that this improvement has contributed to the decrease in mortality from gastric cancer. Comparison of Japanese series with others suggests that diagnosis and treatment of the disease at an earlier stage will result in an even greater increase in 5-year survival outside Japan.

Of the papers studied 56 per cent were excluded from analysis, the majority because the data provided about 5-year survival were insufficient or the survival calculations inappropriate. Results of survival after operations for gastric cancer should be calculated and presented in a standard manner.

Role of splenectomy and distal pancreatectomy in curative surgery for gastric cancer

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Between January 1980 and December 1989, 188 patients with gastric cancer (cardia excluded) underwent operation. Of this group, 133 patients underwent operation with curative intent. An R₂ resection (Japanese classification) was performed. In 38 patients total gastrectomy was undertaken, indications being tumour location with a 10-cm proximal tumour-free margin. In 24 of these, splenectomy with or without distal pancreatectomy was also performed. Complete lymphadenectomy of the splenic artery is possible without distal pancreatectomy, but removal of the distal nodes and of the nodes of the splenic hilum requires splenectomy.

Nodal involvement after resection was analysed. In 4.6 per cent of cases, positive nodes in the distal third of the splenic artery or in the splenic hilum were the only nodes affected in compartment 2, therefore changing the stage of the disease attributed to these

patients. In 16.6 per cent of the cases, positive nodes were found in the distal third of the splenic artery or in the splenic hilum.

In the whole group of patients, 53 underwent total gastrectomy, of whom 18 patients underwent operation without splenectomy, with a morbidity of 11 per cent and zero mortality. In the group with splenectomy with or without pancreatectomy (35 cases), morbidity was 25.7 per cent and mortality 17 per cent, and in the group with splenectomy and pancreatectomy (21 cases), morbidity was 47 per cent and mortality 28.5 per cent.

These results suggest the need for splenectomy when performing surgery with curative intent for gastric cancer (R_2 resection). The increased morbidity and mortality rates associated with splenectomy/pancreatectomy seem to be dependent on the pancreatic resection, which in our experience is not necessary for complete lymphadenectomy. Therefore, distal pancreatectomy should be reserved for cases in which it is necessary for complete tumour removal.

Extensive versus limited lymph node dissection for carcinoma of the stomach: a 10-year experience

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Three hundred and twenty patients who underwent resection for adenocarcinoma of the stomach between 1981 and 1991 were divided into two groups according to the type of lymphatic dissection performed. An extensive lymph node dissection group comprised 157 patients who underwent R_2/R_3 lymphadenectomy (according to the Japanese Research Society for Gastric Cancer) with routine removal of all locoregional lymph nodes in a standardized fashion by the senior author (F.C.). A limited lymph node dissection group comprised 163 patients who underwent conventional lymphadenectomy, including only perigastric nodes in 105 cases (64.4 per cent) and some N_2 nodes (with staging intent) in the remaining 58 cases (35.6 per cent), during the same period. Postoperative morbidity and mortality rates were evaluated in both groups. Survival curves were constructed by the actuarial life-table method and statistical comparison was made using the Mantel-Cox test. In the extensive and limited dissection groups the incidence of postoperative complications was 22.3 per cent ($n = 35$) and 28.2 per cent ($n = 46$) (P not significant); postoperative mortality rate was 3.8 per cent ($n = 6$) and 7.4 per cent ($n = 12$) (P not significant). Among patients who underwent curative resection (117 extensive dissection and 121 limited dissection) the actuarial 5-year survival rate was 65.4 versus 50.1 per cent ($P < 0.02$); 85.9 versus 82.2 per cent in stage I (P not significant); 66.1 versus 57.4 per cent in stage II (P not significant); and 48.7 versus 29.8 per cent in stage III ($P = 0.02$). It is concluded that extensive node dissection permits a significantly better survival rate in the advanced cases of gastric cancer (stage III) without affecting postoperative morbidity and mortality rates.

Ten-year follow-up of 159 patients with early gastric cancer

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The 10-year cumulative survival rate of 159 patients with early gastric cancer (EGC) assessed by the Kaplan-Meier method at the end of 1989 was 90.6 per cent (excluding operative and other causes of mortality), or 86.3 per cent when operative mortality was included. On univariate analysis there was a significant difference in the survival rates ($P = 0.02$, Mantel-Cox and Breslow tests) between mucosal and submucosal cancers and between patients with and without lymph node metastases ($P = 0.05$), and also between patients aged less than or more than 50 years ($P = 0.02$). The survival rate of patients with non-intestinal type EGC was significantly higher ($P = 0.02$) than of those with intestinal EGC. Resection type (total or subtotal gastrectomy) had no influence on survival.

Using Cox's multivariate analysis with stepwise regression for eight variables (sex, age, depth of invasion, lymph node metastases, presence of ulceration, location, histology, resection) age, depth of invasion, and intestinal-type EGC had the most significant effect on survival.

Eleven patients died from recurrent cancer, and one is alive with a stump recurrence. Other causes of death were metachronous primary

cancer (six patients), cardiovascular disease (two), pneumonia (three), sepsis (one) and unknown (one).

Patients with EGC should be carefully followed over a long period to detect late recurrences and because of the high incidence of metachronous cancers.

Choice of surgical management and results for gastric cancer with complications

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Antral cancer (A zone) is sometimes resectable, the surgical objectives being reducing complications and, if possible, removing the primary lesion.

Of 147 patients with gastric cancer admitted between 1984 and 1988 to our clinic, the lesion was antral in 90 (61.2 per cent) and 72 (80 per cent) of those had complications: antropyloric stenosis (51 patients), bleeding (11), extension of the growth to adjacent organs (eight) and perforations (two).

Of the patients 60 per cent were men aged between 51 and 74 years. On admission five (7 per cent) of the tumours were stage II, 27 (38 per cent) were stage III and 40 (56 per cent) were stage IV.

The following surgical procedures were performed: three (4 per cent) total gastrectomy; 23 (31 per cent) radical gastrectomy; 38 (53 per cent) palliative gastric resection – all of them with gastroduodenal anastomosis – and eight (11 per cent) exploratory laparotomy, with an operative mortality rate of 7 per cent. In the postoperative period, all the patients were treated with 5-fluorouracil.

Of the 56 patients operated on in whom there was long-term follow-up, 21 were alive for 3 years, 12 for 5 years and four for 7 years. Most of them died in the first 2 years.

Considering the physical status of the patients and the staging of the disease, we think that complicated antral cancer can be managed by either minimal operations or operations with a 'radical' aim followed by chemotherapy.

Palliative surgery for gastric cancer: retrospective analysis of 112 consecutive cases

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Between January 1980 and October 1991 we operated on 112 patients with gastric cancer, in which the operation was considered to be palliative. This was assessed by intraoperative criteria (gross tumour left behind) or by pathological analysis of the resected specimen. This group comprised 69 men and 43 women, with a mean age of 63.7 years.

The tumour was located in the antrum in 47 per cent, in the body of the stomach in 22 per cent and its point of origin was undetermined in 16 per cent of the cases (this study does not include tumours of the cardia).

Statistical analysis was performed with the χ^2 test for parametric tabulated data, survival estimates were calculated by the Kaplan-Meier method and survival curves were compared with the log rank test. The surgery performed was: 55 non-resection operations (26 exploratory laparotomies, 27 gastroenterostomies, two jejunostomies); 57 resections (30 subtotal gastrectomies, 27 total gastrectomies).

Surgery was considered palliative because of locally irresectable tumour in 25 per cent, peritoneal metastases in 23 per cent, liver metastases in 18 per cent, other metastases in 40 per cent.

Morbidity rate for non-resection surgery was 10 per cent and mortality rate 7 per cent. For resection surgery morbidity rate was 20 per cent, and mortality rate 10 per cent ($P = 0.20$).

Median survival for the entire group was 7 months, and 1-year survival rate was 18 per cent, with Greenwood confidence interval of 0.062. The non-resection group had a median survival of 4 months, and the resection group 18 months (log rank, $P < 10^{-6}$). The group with locally advanced tumours had a median survival of 18 months, and the group with peritoneal metastases and the group with liver metastases had a 4-month median survival each (log rank, $P = 0.0013$).

In conclusion, palliative surgery is mostly performed for clinical reasons, and each operation should be directed to the patient's best interest. In our series we had a 51 per cent resection rate, and this group of patients fared better (18 month median survival). Morbidity and mortality were statistically similar in these two groups. Patients with locally advanced tumours had a better survival than those with metastatic disease. Patients with peritoneal and liver metastasis had a similarly bad prognosis, whether or not a resection was performed, so a patient known to have such a condition should undergo operation only in the presence of strong clinical reasons (e.g. bleeding, obstruction, etc.).

Advanced gastric cancer using neoadjuvant and postoperative etoposide, Adriamycin and cisplatin chemotherapy

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The aim of the study was analysis of the effectiveness of three-drug chemotherapy (EAP) in the management of advanced gastric cancer based on prospective controlled clinical studies and comparative analyses with other currently applied chemotherapy and chemioimmunotherapy using FAM (5-fluorouracil, Adriamycin, methotrexate), FAM+BCG.

The studies involved 138 patients with histologically confirmed advanced gastric cancer of stages IVa and IVb (Fielding modification of UICC classification).

Patients were randomly assigned to the following therapeutic groups: EAP (30 patients) and nil (29 patients). Twenty-eight patients treated in our clinic over the last 5 years with FAM and 26 patients treated with FAM+BCG were computer-matched.

The patients were paired in terms of prognostic and demographic factors such as age, sex, histological and clinical tumour nodes metastasis stage and the surgical treatment.

In ten patients of a group of 30 treated with EAP, neoadjuvant therapy was applied while in the remaining 20 palliative basic treatment was administered. Partial or total remission of disease following EAP, based on the evaluation of measurable features, was obtained in 16 patients (53 per cent). In a group of ten patients receiving neoadjuvant therapy, second-look surgery was performed in seven cases (70 per cent). This made gastric and regional lymph node resection by extended resection (R₃) possible.

It was observed that EAP chemotherapy had a statistically significant ($P < 0.05$) influence on prolongation of survival as compared with control patients: 66 per cent of patients survived for 14 months. Chemotherapy with FAM and FAM+BCG did not influence survival of patients with advanced gastric cancer.

Surgical treatment of carcinoma of the gastric cardia

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Adenocarcinoma of the gastric cardia is a highly aggressive tumour with rapid metastatic invasion towards the mediastinum and the abdomen: surgical treatment must be related to these peculiar characteristics. Of 66 patients affected by carcinoma of the cardia who underwent surgery between 1981 and 1990, resection was possible in 56 (85 per cent). In 28 patients proximal gastrectomy with distal (26) or subtotal (two) oesophagectomy (OGR) was performed. In the remaining 28 patients total gastrectomy with distal oesophagectomy (TG) was performed. In 33 patients (59 per cent) combined thoracotomy and laparotomy (L+T) was used; in 23 laparotomy only was used. Three patients were stage I, nine stage II, 31 stage III and 13 stage IV, with homogeneous distribution in the two groups. There were 11 (20 per cent) deaths in the patients undergoing resection. The 3- and 5-year survival rates were 25 and 18 per cent, respectively. There are significant differences in survival rate between patients with stage I-II tumours and those affected by stage III-IV tumours. There are no significant differences between the two groups in terms of operative mortality, complications and long-term survival. The TG group showed improved survival of patients with stage I-II tumours compared with the OGR group (5-year survival 100 versus 58 per cent; P not significant). TG combined with L+T improved survival compared with TG with L only ($P < 0.05$). In patients with stage III-IV tumours there were no differences in survival between the two groups.

TG combined with L+T is the procedure of choice in patients with adenocarcinoma of the cardia in stages I-II. For stages III-IV, surgery is palliative; OGR with subtotal oesophagectomy provides a suitable alternative to TG for good prophylaxis of anastomotic recurrences.

Surgical treatment of carcinoma of the cardia

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During a 10-year period, 50 patients, 43 men and seven women with a mean age of 67 (range 42-84) years, underwent surgical resection for carcinoma of the cardia: 42 adenocarcinomas, two undifferentiated, two carcinoids and one sarcoma. Surgical procedures included 20 total gastrectomies with partial oesophagectomy and 30 partial oesophagogastrastomies. The approach was abdominal with right thoracotomy in 16 cases, abdominal in 14 cases, left thoracotomy in 13 cases and abdominal with left thoracotomy in six cases.

Postoperative tumour node metastasis classification showed: four stage I, nine stage II, 20 stage III and 17 stage IV. Lymph node involvement was present in 36 cases (72 per cent).

Five patients died during the postoperative period (mortality rate 10 per cent). Morbidity was essentially due to pulmonary complications (28 patients; 56 per cent) leading to death in two cases, with no correlation to preoperative findings or the type of procedure used. Anastomotic leakage occurred in four cases, with two deaths. Actuarial survival rate was 55 per cent at 1 year, 33 per cent at 2 years, 24 per cent at 3 years and 18 per cent at 5 years (30 for stages I-III, nil for stage IV). Five-year survival was 26 per cent after total gastrectomy and partial oesophagectomy, and 8 per cent after partial oesophagogastrastomy (P not significant).

It is concluded that young patients, with stage I or II disease, should undergo total gastrectomy with oesophagectomy and reconstruction by Roux-en-Y or colonic replacement (thoracic or cervical anastomosis). In patients over 75 years old, with high operative risk, or with stage III-IV disease, we prefer partial oesophagogastrastomy by the left thoracic approach with circular phrenotomy.

Surgical approaches for adenocarcinoma of the gastric cardia

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Between January 1986 and October 1991, 65 patients underwent surgical treatment for adenocarcinoma of the cardia at the General Surgery Department of Istanbul Medical Faculty. A group of 39 patients (60 per cent) having resectable tumours were evaluated. Surgical techniques, morbidity, mortality, and survival rates were recorded.

The procedure performed depended on tumour size, local spread and distal and proximal margins of tumour. Standard transthoracic oesophagogastrastomy and oesophagogastrastomy was performed in 11 patients, transhiatal oesophagectomy and partial proximal gastrectomy in 11 and transabdominal oesophagogastrastomy in 17 patients. There was no significant difference between the groups in age, sex and tumour node metastasis (TNM) staging. All patients had stage III tumours.

Morbidity rate was higher in the transhiatal group (five of 11) than in the transabdominal group (three of 11). There was no morbidity in the transthoracic group. Mortality was higher in transhiatal (three of 11) than in the transthoracic group. Average postoperative hospitalization was 11.6 days. Overall 1-year and 2-year survival rates were 42 per cent and 8 per cent respectively. The difference between the survival rate of each group was not statistically significant. Although the morbidity rate was found to be high after transabdominal and transhiatal resection, and mortality was high in the transhiatal group in this study, the differences were considered to be insignificant in view of individual features in these cases.

In conclusion, transabdominal, transthoracic or transhiatal approaches may be chosen in the surgical treatment of carcinoma of the cardia, according to the size and local spread of tumour.

Gastric stump cancer

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The aim of the study was to evaluate our experience with the diagnosis and surgical management of gastric stump cancer (GSC). The study reports on 41 patients diagnosed as suffering from GSC.

Different parameters were analysed. The mean age was 59 (range 33–75) years and comprised 39 (95 per cent) men and only two (5 per cent) women. In 32 cases (78 per cent) a Billroth type II partial gastrectomy had been performed previously and a Billroth I in nine cases (22 per cent). The interval from surgery to diagnosis was 21 (range 6–40) years, but in older people the interval was shorter (14 years, $P < 0.001$). Gastroscopy was the diagnostic method in 30 patients (73 per cent). Four patients (10 per cent) with unsuspected endoscopic abnormalities had positive biopsies.

Following the tumour node metastasis (TNM) classification the tumour stage was I in 22 per cent (nine cases); II in 19 per cent (eight cases), III in 27 per cent (11 cases) and IV in 32 per cent (13 cases).

All patients underwent surgery. Resection was possible in 29 patients (71 per cent). Partial gastrectomy was performed in ten cases (24 per cent) and total gastrectomy in 19 cases (46 per cent). The overall 5-year survival rate was 13 per cent.

We recommend annual endoscopic screening and multiple biopsies for all patients who have undergone gastric resection, in order to detect early GSC. Partial gastrectomy with Roux-en-Y reconstruction is recommended for early GSC and total gastrectomy (if possible) for advanced GSC.

Results of 15-year multicentre prospective study on early detection of gastric cancer and the effect of surgical and chemoimmunotherapeutic treatment

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The results of early gastric cancer detection and the improvement of gastric cancer treatment in terms of 5-year survival were analysed based on screening, questionnaire and endoscopic examinations in 47212 patients. Controlled prospective studies in 1548 patients between 1976–1986 and 1986–1990 in the nine leading academic centres in Poland within the 'Polish Experiment' sponsored by a Polish government grant no. VI. CPBR 11.5 were analysed.

The applied model for the improvement of gastric cancer detection resulted in an increase of early gastric cancer detection from 3.5 to 31.5 per cent in 1990.

The results of studies on the effectiveness of gastric cancer treatment show that the extended gastric resection (type R₁–R₃) and the addition of chemoimmunotherapy FAM+BCG, 5-FU+BCG resulted in an improvement of the total 5-year survival rate from 19.7 to 26.7 per cent in two comparable study groups.

In advanced gastric cancer based on the clinical and pathological stage according to the Fielding modification of UICC (Union Internacional Contra le Cancrum) it was observed that in stage II, the 5-year survival rate was increased by 28.6 per cent, in stage III by 11.6 per cent and in stage IV (palliative resection) by 23.8 per cent.

This report presents characteristics of the model for early gastric cancer detection and the applied chemoimmunosurgical method of treatment.

Multicentric early gastric carcinoma

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Clinical aspects and biological behaviour of multicentric early gastric cancer (EGC) were studied in 11 surgically treated patients. Of a total series of 360 patients with gastric cancers, 50 EGCs were treated in this institution during the past 10 years. Eleven (22 per cent) were found to be multicentric. The mean age at diagnosis was 69 years and the male:female ratio was 8:3. Abdominal epigastric pain was present in all 11 cases and all were treated by subtotal gastrectomy. Six

tumours were located in the antrum, and five in the body of the stomach. According to the Laurén histological classification, eight cases were intestinal, two were diffuse and one was mixed. The most frequent macroscopic appearance was the excavated type (JSGE type III) in six cases; type II occurred in three cases, and type I in two cases. Mean follow-up was 4 years. There was one recurrence as a gastric stump cancer among the multicentric EGC compared with none in patients with unifocal EGC. Five-year actuarial calculated survival was 83 per cent for patients with multicentric EGC, and 86 per cent for unifocal EGC.

Multicentric growth of neoplastic cells is not rare in EGC, being more frequent in our series of EGC (22 per cent; 11 of 50) than in invasive cancers (4 per cent; 13 of 310). This suggests that it is advisable to perform total gastrectomy for EGC located in the proximal two-thirds of the stomach, provided that acceptable morbidity and mortality rates can be achieved.

Results of surgical treatment for gastric cancer penetrating into neighbouring organs or having distant metastases

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We report our experience of combined and extended gastric cancer operations.

During the years 1974–1986, 1259 gastric cancer patients aged 24–89 years (30 per cent between 60 and 70 years) underwent operation. There were 796 radical operations comprising 406 subtotal distal resections (SDR) (51 per cent), 358 total gastrectomies (TG) and 32 proximal subtotal resections (PSR) (4 per cent).

Combined operations were performed in 453 patients, 32 per cent SDR, 87 per cent TG and 59 per cent PSR involving multiple organs. The organs most frequently resected were the spleen, pancreas, transverse colon, left lobe of the liver and the diaphragm. In six patients Whipple's procedure was performed; 64 cases with distal subtotal pancreatectomy were in this group.

Extended operations were performed in 86 cases where solitary distant metastases were present. We always perform prophylactic lymphadenectomy along the hepatic artery and from the hilus of the liver.

The postoperative mortality rate was 4.9 per cent. The 5-year survival rate without regional metastases was 59 per cent, with regional metastases 31 per cent and with distant metastases 8 per cent.

Construction of a jejunal pouch using stapling devices in patients undergoing total gastrectomy

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Twenty-eight patients underwent total gastrectomy with construction of a jejunal pouch. The suggestion was that patients with a pouch should be able to eat larger meals. This was confirmed by the patients and there were no complaints of regurgitation. Cachexia was not observed in the disease-free period of the patients who died nor in the survivors.

The jejunum was transected such that a Roux-en-Y anastomosis could be performed. Using a 20–25-cm loop of jejunum, a pouch was constructed with two or three GIA (US Surgical) stapling devices. This pouch was then anastomosed to the oesophagus using the EEA stapler (US Surgical). The opening in the pouch was closed manually with absorbable sutures.

There was one postoperative death (myocardial infarction) in the 28 patients (mean age 63 years). The male:female ratio was 3:1. Twenty-two patients died with a mean (range) survival of 17 (2–67) months. Five patients are alive at a mean of 48 (32–108) months. There were no postoperative leaks. Wound infections were not observed. The operation time was not significantly longer than a simple manual oesophagojejunal anastomosis. The longest living patient underwent a reoperation after 1 year for intermittent volvulus of the jejunum near the pouch.

It appears that these patients can eat larger meals and do not have typical complaints such as regurgitation or postprandial pain. Construction of a pouch is recommended in patients having a total gastrectomy despite the poor prognosis with regard to long-term survival.

Multiple trauma in patients of 65 years and over: injury patterns and outcome

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In a consecutive series of 616 patients with multiple injuries, 86 were aged ≥ 65 (mean 72.1) years. This group of 'old' patients was compared with the remaining 530 'young' patients (mean age 31.3 years). In the old group, survivors and non-survivors were profiled. In general, the injured old patient was a pedestrian hit by a car or a motorcycle or someone who had simply fallen at home. Despite the fact that the mean injury severity score (ISS) was significantly lower in the old group (33.2 versus 42.1; $P < 0.001$), the mortality rate was significantly higher (18 versus 7.6 per cent; $P < 0.05$). We found that in the elderly injured the ISS and pre-existing disease were not predictive of survival. However, brain injury with unconsciousness and the need for early intubation followed by long-term assisted ventilation were predictive of poor survival ($P < 0.001$). Of the survivors, 76 per cent were able to return home again within 6 months. As the final outcome in the elderly is no worse after multiple trauma than after other important emergency procedures, an aggressive treatment including urgent operative fixation of major fractures is justified.

Radical surgery for colorectal cancer in the elderly

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To evaluate chances and risks of radical surgery in elderly patients, data of all operations for primary colorectal cancer in a period of 20 years were analysed retrospectively. Patients over 75 years of age (group 1) were compared with those of 75 years and younger (group 2).

Of all patients 11.9 per cent (223 of 1876) were over 75 years. Resection for cure (R_0) was possible in 68.6 per cent (153) of group 1 and 72.7 per cent (1202 of 1653) of group 2 (P not significant). Tumours of the right colon were slightly more frequent in the elderly (23.3 per cent, $n = 52$ versus 19.3 per cent, $n = 319$; P not significant). No differences could be found with regard to Dukes' classification, tumour characteristics, and complications, except cardiopulmonary complications. The latter were significantly more frequent in group 1 than in group 2 (17.5 per cent, $n = 39$ versus 7.9 per cent, $n = 130$; $P < 0.0001$). The same was true for operative mortality rate (13.9 per cent, $n = 31$ versus 6.4 per cent, $n = 106$; $P < 0.0001$). Five-year survival rates (Kaplan-Meier) for the entire groups 1 and 2 were 31.1 per cent and 46.6 per cent. Following R_0 resection the corresponding figures were 45.1 per cent and 62.3 per cent. These data are not corrected for age. Median survival after $R_{1/2}$ resection was 8.8 months in group 1 and 8.1 months in group 2.

Elderly patients can profit by radical surgery as well as younger ones. The increased risks of cardiopulmonary complications and operative mortality should be considered individually in every case but it is not justifiable to exclude patients from radical resection of colorectal cancer on grounds of age alone.

Operation in patients over 80 years with colorectal or gastric cancer

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One hundred and three patients of 80 years of age or older were operated on for colorectal cancer (CRC, $n = 80$) or gastric cancer (GC, $n = 23$). Surgery was considered as curative in 66 CRC and in ten GC cases. Distant metastases were present in nine cases of CRC, and in ten cases of GC. The purpose of this study was to improve selection of patients who might benefit from surgery.

Postoperative mortality rate was 8 per cent overall. It was higher in GC than in CRC ($P = 0.05$). It was not influenced by age or emergency procedure. American Society of Anesthesiologists score and palliative procedures had a marginally significantly detrimental

influence ($0.05 < P < 0.08$). Morbidity was correlated only with palliative procedure.

Overall 5-year survival rate was 23 per cent for CRC, and 10 per cent for GC ($P = 0.001$). After colorectal surgery long-term survival was observed even in advanced disease: 13 patients are alive more than 5 years after surgery (the serosa was invaded in four cases and lymph node involvement was present in three cases). Most deaths were not related to widespread malignancy. One year after surgery the survival curve of patients was similar to the survival curve of an age- and sex-matched general population. After gastric carcinoma, all patients but two died within 1 year. All deaths but one were related to widespread malignancy. The two long-term survivors (4.5 and >5 years) had early gastric carcinoma.

Our results suggest that postoperative mortality rates are acceptable in elderly patients operated on for CRC or GC. Advanced diseases are more frequent in GC than in CRC so that the indication to operate should be more restricted for GC.

Colectomy for left-sided large bowel obstruction secondary to cancer in patients over 75 years

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Colectomy for carcinomas obstructing the left colon both relieves the obstruction and removes the tumour. This avoids the morbidity of a series of operations. This study assesses the results of colectomy for obstructing tumours in elderly patients.

Between 1985 and 1991, 37 patients (25 women, 12 men), mean age 83.9 (range 75–93) years underwent operations for left-sided obstructions. A colectomy was performed in 22 patients (73 per cent): eight without anastomosis (Hartmann's operation) and 19 with immediate anastomosis. Of the remainder, seven had a palliative colostomy, two had laparotomy only and one had laser dis-obstruction. Of these last ten patients, eight had advanced disease and two had contraindications to general anaesthesia.

The total mortality rate was 22 per cent. The mortality rate after colectomy without anastomosis was 25 per cent (two patients), and with immediate anastomosis it was 21 per cent (four patients). Three of the deaths after colectomy were from general complications and the rest from carcinomatosis. The fistula rate was 16 per cent (no deaths). No patient having a Hartmann's operation has had restoration of intestinal continuity.

In these patients, colectomy is possible in 73 per cent of cases and can be performed with a mortality rate similar to colostomy, which is also similar to colectomy in younger patients. Colectomy improves patient comfort compared with palliative colostomy.

The high rate of fistula formation may be reduced by on-table colonic washout, which has not been used in this series.

In summary, colectomy is feasible and gives satisfying results in elderly patients presenting with left-sided large bowel obstruction.

Quality of life after open heart surgery on patients of 75 years of age or older

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Without doubt, open heart surgery can be performed even in patients of 75 years of age or older, but it is not clear whether this is justified. Between 1988 and 1990, 46 patients aged 75 or older underwent open heart surgery in our department (27 men, 19 women). The mean age was 76.4 (range 75–80) years. Thirty-three patients had coronary artery disease, 11 underwent aortic valve replacement and two underwent mitral valve replacement.

We followed up 35 patients. Seven died after operation and four did not reply to a questionnaire. General practitioners were also contacted.

Twenty-three patients had no complaints, ten patients had angina with moderate or high level exercise and two had angina at rest. Three felt no change or worse than before the operation. Nine patients were able to perform normal activities, 23 were able to

undertake long-distance walks or cycling tours and three were able to make long-distance journeys by aeroplane or ship.

The general practitioners' questionnaires gave the same results. Most of these patients have a better quality of life after open heart surgery.

Vascular surgery in the elderly

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Between 1 January 1988 and 31 August 1991, surgical revascularization of the aorta and the lower limbs was performed on 24 men and 18 women aged ≥ 75 years; the median age was 80 (range 75–84) years. In all cases, surgery was essential owing to ischaemia of the lower limbs (stage III or IV, Fontaine's classification) (37 patients) and ruptured abdominal aortic aneurysm (five patients). No major amputations were done immediately in the patients with peripheral ischaemia stages III and IV. Peripheral vessel operations were performed under locoregional anaesthesia. The operations performed were distal femoropopliteal bypass with saphenous vein *in situ* (30 patients). Patients with proximal vessel disease underwent extra-anatomical bypass if possible under general anaesthesia because of their poor general condition (seven cases). Ruptured infrarenal aortic aneurysm also needs a general anaesthetic and represents a high surgical risk (five patients). Of the 42 patients, 38 showed good immediate functional results and there were four perioperative deaths (one after surgery for ruptured aortic aneurysm, one after aortobifemoral bypass for ischaemia stage IV, one after femorodistal bypass for septic gangrenous foot and one after a surgical procedure for a femoral aneurysm). In the 38 patients with a good immediate result, we noted six secondary blockages of the bypass within a period of 5–18 months, two of which were cleared successfully. The other four patients have had lower-limb amputation.

In conclusion, good results from the venous *in situ* bypasses were obtained in elderly patients with peripheral ischaemia. Extra-anatomical bypass gave good functional results and made it possible to avoid major amputation. Blockage of the bypass had a poor prognosis. Ruptured aortic aneurysm also has a very poor prognosis. Such patients should therefore undergo surgery before rupture or suspicion of rupture. The development of endovascular surgical techniques makes it possible, while reducing the postoperative risk, to enlarge the field of action of the surgeon in critical ischaemia of the lower limbs.

Groin hernias in patients of 80 years or over

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Most surgeons advise operation for hernia in old people to avoid strangulation. The posterior wall of the inguinal canal is very weak in these patients. We recommend that it be reinforced using a prosthetic implant and use wire mesh as it is resistant to infection. Whatever the type of anaesthetic used, the problem in these patients is to avoid postoperative pain, bronchopulmonary complications and loss of independence.

This series includes 102 patients (26 simultaneous bilateral repairs) with a mean age of 84 years. Only 20.5 per cent presented with a strangulated hernia. There was a 7 per cent incidence of wound infections, all of which responded to local treatment with no relapse. The postoperative mortality rate has been 2.9 per cent (owing to cardiorespiratory complications) over the past 3 years. The mean length of hospital stay was 8 days. Recurrence was rare (2 per cent); these patients underwent reoperation with no further recurrence.

These results show that it is reasonable to offer elderly patients hernia repair. The use of a prosthetic material strengthens the posterior wall of the inguinal canal.

Carotid endarterectomy in patients aged 75 years and older

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To evaluate the role of carotid surgery in patients aged 75 years and older, a review was carried out of 1702 carotid endarterectomies performed on 1493 patients between 1976 and 1990. There were 154 patients (10 per cent of the whole series) aged 75 years and older (175 endarterectomies, group 1), including 29 octogenarians, *versus* 1339 patients under 75 years of age (group 2). There were more women in the elderly age group (53 per cent) than in the younger one (38 per cent). Symptoms, risk factors, operative outcome and follow-up data of the two groups were compared. The risk profile was similar for the two age groups, with the exception of coronary heart disease, which was more common in the older patient group (60 per cent had had previous infarction *versus* 44 per cent). The indication for carotid endarterectomy was different in the two age groups: 41 per cent of group 2 underwent prophylactic thromboendarterectomy for high-degree stenosis, while only 20 per cent of group 1 had asymptomatic carotid disease. In group 1, 6 per cent of the patients had carotid endarterectomy after recovering from a mild stroke *versus* 2 per cent in group 2. Angiography revealed bilateral carotid disease in 48 per cent of the group 1 patients (including 15 per cent with contralateral occlusion), while lesions were less diffuse in group 2 patients (25 per cent bilateral stenosis, 10 per cent contralateral occlusion). Operative morbidity included a 2 per cent ipsilateral neurological deficit in group 2 *versus* 2.3 per cent in group 1. Half of the postoperative neurological events were transient. Half of the complete strokes were fatal.

The operative mortality rate was 2 per cent for the younger age group compared with 4 per cent for the older age group. The cause of death was cardiac in 60 per cent of the older patients and 40 per cent in the younger ones, and was stroke-related in 30 per cent of group 2 *versus* 15 per cent in group 1.

The long-term follow-up ranged from 6 months to 12 years (mean 5 years). The 5-year survival rate was 78 per cent for group 2 patients and 61 per cent for group 1 patients. Cardiac disease was the most common cause of late death. Most of the survivors remained stroke-free (5-year stroke incidence of 7 per cent, with half of the late neurological events occurring in the territory of the non-operated side).

It is concluded that the elderly patient group is characterized by more severe, generalized atherosclerosis, accounting for an increased cardiac risk. Carotid endarterectomy in patients aged 75 years and older remains valuable as a stroke-preventing procedure, with an acceptable combined stroke and mortality rate.

Coronary reoperation in the elderly

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In a retrospective analysis of 115 patients who underwent coronary reoperation between 1984 and 1989 we studied the influence of age on the perioperative morbidity and mortality rates and on the long-term results. The mean age of the population was 59.4 years; 55 patients were below 60 years, 52 between 60 and 70 years and eight patients were over 70 years old. The distribution of risk factors was similar to that of other populations suffering from coronary heart disease. The mean time between first and second coronary operations was 7.1 years. Complete revascularization at reoperation could be obtained in only 20.9 per cent (24 patients). A mean of 1.9 vein grafts were implanted. The perioperative mortality rate (30 days) was 5.2 per cent (six patients) for the whole group, whereas the highest mortality rate was in the eight patients aged over 70 years, with two deaths. The incidence of perioperative myocardial infarction was higher in the elderly patients compared with the whole group. After a mean time of 39 months all patients were re-examined; 14 patients (12.2 per cent) had died. Most of the deaths were cardiac related. The cumulative survival rate was 91 per cent after 1 year, 90 per cent after 3 years and 88 per cent after 5 years. We found no statistically significant difference in the survival rate between the different age groups. The results obtained from our retrospective study showed that age influenced the perioperative results. On long-term follow-up, even patients aged over 70 years had benefited from coronary reoperation.

Carcinoma of the oral cavity and the oropharynx in patients over 75 years of age

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The results of a 15-year retrospective study of the influence of age on the incidence and survival of 50 patients aged ≥ 75 years with oral or oropharyngeal carcinoma were analysed. Two-thirds of the patients were aged 75–79 years and one-third were aged 80–85 years. The male:female ratio was 1.5:1. Only one-third of the patients were smokers and/or drinkers. One-third suffered from serious concomitant systemic disease (cardiac, cardiovascular, respiratory, diabetes).

Half of the tumours appeared in the tongue, and 15 per cent in the cheek. Lymph node metastases occurred in 30 per cent regardless of the size of the primary tumour. Half of the latter were well differentiated, 40 per cent moderately and only 10 per cent poorly differentiated or undifferentiated.

Half of the patients were treated either by surgery or radiotherapy and the other half by a combination of both. Surgery was usually limited to a local resection with primary closure or skin grafting. Only one-quarter underwent major surgery on tumour and neck with primary flap reconstruction.

The 3-year survival rate was roughly 50 per cent. The younger, female and healthy patients did better in general.

In conclusion, older patients with oropharyngeal carcinoma present some interesting differences from younger ones. These possibly contribute to the better prognosis for younger patients.

Results of surgical treatment of patients over 75 years of age with colorectal cancer

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The elderly population, particularly those over the age of 75 years, has been increasing steadily, making surgery in this age group a continuous challenge. Between 1980 and 1989, 87 patients over 75 years of age were operated on for a colorectal carcinoma in our hospital service. There were 46 men and 41 women, with a mean age at operation of 80.4 (range 75–88) years. Fifty-one (59 per cent) patients were between 75 and 79 years, and 36 (41 per cent) were over 80 years of age; the male:female ratio was almost equal. There were 48 colon and 39 rectal cancers. According to the classification of the American Society of Anesthesiologists (ASA), 37 (43 per cent) patients were grade II, 42 (48 per cent) grade III and eight (9 per cent) grades IV and V. Fifty-nine (68 per cent) patients were operated on electively; 54 (62 per cent) were operated for cure; the resectability rate was 74 per cent (64 patients). Fifty-five (63 per cent) patients were operated on in the past 5 years and 27 were over 80 years of age. Our mean overall postoperative mortality rate was 9 per cent (eight patients), four operated on to be cured and the other four undergoing a palliative procedure. Five were undergoing an elective operation and the other three an emergency procedure (colostomy); of these three, two were over 80 years of age in ASA grade II. Some 87.5 per cent of the deaths were related to systemic organ failure; our mean overall postoperative morbidity rate was 20 per cent (17 patients). The mean survival time was 27 months; the actuarial survival curve showed a 40 per cent survival rate at 3 years and 27 per cent at 5 years.

Our data suggest and support the view that surgery is safe in the elderly with colorectal cancer, and a curative procedure should always be tried, even in emergency situations.

Digestive tract surgery in the aged

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During the period from 1 January 1985 to 30 September 1991, a retrospective study was performed on 274 patients who underwent gastrointestinal surgery. The mean (range) age in this series was 82.1 (75–94) years with a sex ratio (female to male) of 1.9 (180 women and 94 men). This group of patients represents 10.6 per cent of the patients who underwent digestive surgery during the same period. The average hospitalization was 18.8 days. A total of 51 patients (18.6 per cent) had emergency surgery within 24 h after admission while in 223 patients (81.4 per cent) the operation was performed

after 24 h. There were 94 cases of colorectal surgery (mortality rate nine of 94; 10 per cent), 76 cases of general digestive surgery (appendectomy, hernia repair, haemorrhoidectomy, Zenker resection etc.) (mortality rate one of 76; 1 per cent), 63 cases of biliopancreatic and splenic surgery (mortality rate two of 63; 3 per cent), 20 cases of gastric surgery (mortality rate five of 20; 25 per cent), 13 laparotomies for peritoneal carcinomatosis (mortality rate ten of 13; 77 per cent) and eight laparotomies for mesenteric infarction and small bowel necrosis in strangulated hernia (mortality rate eight of eight; 100 per cent). There was a significant difference (χ^2 test) of mortality between surgery for mesenteric infarction, small bowel necrosis and peritoneal carcinomatosis (18 of 21; 86 per cent) and for colorectal, gastric, biliopancreatic, splenic, perineal and general digestive surgery (17 of 253; 6.7 per cent). There was no statistical difference in terms of mortality rate when supramesocolic surgery was compared with inframesocolic surgery (seven of 83; 8 per cent *versus* ten of 170; 5.9 per cent). There was a significant difference in mortality rate between emergency surgery (17 of 51; 33 per cent) and elective surgery (18 of 223; 8.1 per cent). In elective surgery, a significant decrease in mortality rate was observed when cases of peritoneal carcinomatosis were excluded (eight of 210; 3.8 per cent *versus* 10 of 13; 77 per cent). The general morbidity rate in this series was 24 per cent (66 of 274); 5.8 per cent (16 of 274) for local complications and 18.2 per cent (50 of 274) for general complications. Local and general infective complications represented 9.1 per cent (25 of 274).

In conclusion, mean hospitalization was not prolonged and social reintegration was obtained in 94 per cent. Mortality rates were high in emergency surgery and in gastric surgery. Mortality was prohibitive in surgery for mesenteric infarction and peritoneal carcinomatosis. Surgery for strangulated hernia with bowel necrosis had a very poor prognosis; in contrast there was no mortality for elective hernia repair. The results in colorectal, biliopancreatic and general digestive surgery were acceptable.

Incisional hernias in patients of 80 years or over

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Incisional hernias in elderly patients require careful treatment. The abdominal wall in very old patients, especially those with incisional herniation, must be correctly treated with artificial materials.

This series includes 30 patients aged over 80 years with incisional hernias. The repair was reinforced with an artificial prosthesis of wire mesh, which is very resistant to infection.

The mean age of the patients was 82 years. Only 10 per cent of patients presented with strangulation. The mean length of hospital stay was 20 (range 10–45) days. The postoperative mortality rate was 7 per cent (two patients, each because of heart attack, kidney failure and cardiorespiratory reasons). There were no recurrent hernias. There was a 10 per cent incidence of wound infection, but all patients responded to local treatment.

These patients benefit from careful preoperative and postoperative attention. Good functional results were obtained with excellent abdominal wall integrity and improved respiratory function, without gastrointestinal side-effects. The use of wire mesh as an artificial implant is recommended as it is resistant to infection.

Management of advanced rectal cancer in the elderly: surgical treatment compared with endoscopic laser vaporization

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Surgery of advanced rectal cancer is often limited by palliative efficacy and a high morbidity rate. Endoscopic techniques have become more effective with the application of laser therapy. This study aimed to analyse results and side-effects of both treatment modalities in the elderly.

Between 1985 and 1991, 48 patients over 75 years of age were treated for locally advanced rectal cancer. In 36 cases surgical operations were performed, 21 of which were curative as assessed by histopathology. Laser vaporization was performed in 12 cases. The

median age was 77 years (surgical group) *versus* 78 years (endoscopic group). The basic clinical characteristics were the same in both groups.

The median survival time following curative operation was 19 months ($n = 21$), compared with 7 months in the palliative group ($n = 15$). The morbidity rate (leakage, pneumonia) was significantly higher in the palliative group (38 per cent) than in the curative group (18 per cent). There was one fatal complication following potentially curative and two following palliative operations. Local recurrence with stenosis occurred in six cases, all of which were successfully treated with endoscopic laser therapy.

The median survival time following laser therapy was 8 months

($n = 12$) with a median stenosis-free interval of 3.5 months. A second (or more) laser recanalization was successful in eight patients with recurrent tumour stenosis. A colostomy could not be avoided in two cases when laser therapy finally failed owing to rapid tumour growth. The most frequent complication in this group was bleeding following vaporization ($n = 5$), which could be easily controlled by laser coagulation. There was no fatal complication in this group.

For attempted cure, surgical treatment of advanced rectal cancer is the therapy of choice in the elderly. Endoscopic laser vaporization of the malignant stenosis appears to be a potent therapeutic tool with few complications. It is therefore a welcome addition to conventional surgery for palliation.

Low pubic tubercle predisposes to inguinal hernia

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The aim of this study was to test the hypothesis that the height of the pubic tubercle in relation to the iliac bones is a determining factor in the development of inguinal hernia.

The height of the pubic tubercle, body-weight and height were measured in 20 healthy volunteers and in 154 men with inguinal hernia. Volunteers were men older than 60 (median 66, range 60–85) years. This age was selected because the likelihood of developing a hernia in their remaining life is less than for a younger group. The patients had a median age of 52 (range 31–80) years and presented with direct or indirect inguinal hernias either unilaterally or bilaterally. Comparisons were made between the controls and hernia patients and between the controls and a subgroup of 42 patients older than 60 years, in order to have age-matched groups. The height of the pubic tubercle was determined by measuring the distance of the tubercle, identified by inguinal palpation, to a horizontal line drawn between the most anterior aspect of the iliac crests, i.e. the iliac spine.

The mean (s.d.) distance of the pubic tubercle to the bicrestal line was 7.0(1) cm in the control group. Body-weight was 71(10) kg and height was 166(9) cm. Patients with inguinal hernia had a significantly lower pubic tubercle, lying at 9.0(2) cm from the bicrestal line ($P < 0.001$). Body-weight (72(11) kg) and height (166(7) cm) were similar to the control group. The height of the tubercle was poorly related to body-weight ($r = 0.20$, $P < 0.05$) and not related to body height. The subgroup of 42 patients older than 60 years was of similar body-weight and height to the control group, and had a pubic tubercle at 9.0(2) cm from the bicrestal line, a distance identical to that of the whole group of patients and significantly longer than that of controls ($P < 0.001$).

The distance of the pubic tubercle to the bicrestal line is greater in individuals who develop inguinal hernia than in normal subjects. This finding suggests that a low pubic tubercle is an important factor in the development of hernia of the inguinal region, probably because it causes a weaker inguinal triangle.

Expanded polytetrafluoroethylene patch versus polypropylene mesh for the repair of contaminated abdominal wall defects

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Contaminated abdominal wall defects continue to be a major problem for both patients and surgeons. The lack of sufficient tissue may require the insertion of prosthetic material. Polypropylene (PP) mesh is still the most widely used material for this purpose, although its propensity to induce extensive visceral adhesions and erosion of the skin or bowel is well known.

Expanded polytetrafluoroethylene (ePTFE) patch has better mechanical properties and has a low risk of infection. Therefore in this department ePTFE was used to repair contaminated abdominal wall defects in three patients. In one patient the postoperative course was uneventful. In the other two patients the patch had to be removed because of wound sepsis and because the patch disintegrated.

In an experimental study contaminated abdominal wall defects created in Wistar rats were repaired with either ePTFE patch ($n = 21$) or PP mesh ($n = 21$). Wound infection occurred in 16 rats in the ePTFE group and in 14 rats in the PP group. Two rats in each group died. Two rats died as a result of peritonitis in the ePTFE group. In the PP group one died as a result of ileus and one from peritonitis. Incisional hernia was found significantly more frequently in the ePTFE group (13) compared with the PP group (three). Fistula formation was found in only three PP rats, whereas adhesion formation was more pronounced in PP rats.

It is concluded that the ePTFE patch is unsuitable for the reconstruction of contaminated abdominal wall defects and that PP mesh is more suitable, although this material also carries a high risk of complications.

Personal interpretation of the Shouldice repair for inguinal hernia

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The Shouldice repair of inguinal hernia has several features. One is repair of the transversalis fascia by means of continuous sutures to achieve a strong repair of the posterior wall of the inguinal canal.

The purpose of this paper is to discuss this surgical aspect, based on a 10-year experience of the technique.

Once the spermatic cord is dissected and freed from the cremaster muscle, which is wholly excised, the transversalis fascia appears as the posterior wall of the inguinal canal. It is a thin anatomical structure. Its strength appears uncertain. It is opened between the pubic tubercle and the deep inguinal ring and dissected on its posterior face to reach down to the deeper part of the inguinal ligament and up to the posterior part of the conjoint tendon or falx inguinalis which is usually fibrous. Thus, this dissection is the best way to reach the only two strong anatomical structures able to support the sutures effectively.

The first continuous suture must take the inguinal ligament and the falx inguinalis directly, rather than the thin sheets of the transversalis fascia. If not, it would be more difficult to take the two strong structures with the next continuous suture.

Only the two strong structures must be taken by the sutures; the anterior part of the conjoint tendon, which is often muscular, may be weak.

In my opinion, the transversalis fascia is only a means to reach the strong anatomical structures rather than a useful anatomical element used in the Shouldice repair of inguinal hernia.

Long-term results of prosthetic repair of recurrent inguinal hernia using Prolene sheets

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The incidence of second recurrence after repair of a recurrent inguinal hernia has been reported as approximately 30–40 per cent, and has been stated to be due to defects of the transversalis fascia. In a retrospective study the complication rate was evaluated in 30 patients who underwent prosthetic repair of recurrent inguinal hernia using a Prolene (Ethicon) sheet and a modified Shouldice technique with subcutaneous placement of the spermatic cord. In 18 patients it was the first recurrence, in six patients the second, and in six patients the third. Four years after implantation of the Prolene sheet, all patients underwent physical examination and ultrasonography of both groins, and answered a standardized questionnaire. Early postoperative complications included a haematoma in three patients and in one patient a transiently swollen scrotum. Thirteen patients complained of temporary loss of sensation in the groin region which lasted for more than 4 months after surgery in one patient. Another 13 patients complained of wound pain, persisting for not longer than 3 months. After 4 years none of the patients had testicular atrophy, one patient had definitive ilioinguinal nerve injury and in two patients a femoral hernia was observed. Because of the decreased incidence of recurrence and the low complication rate, prosthetic repair of recurrent hernias, using a Prolene sheet and a modified Shouldice technique, is to be recommended in the treatment of recurrent inguinal hernia.

A new patch for the reconstruction of abdominal wall defects

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The purpose of this study was to develop an abdominal wall prosthesis which anchors itself firmly to the abdominal wall on one side and which prevents adhesion formation on the other.

A new porous patch was designed with a large pore size on one side in order to allow ingrowth of fibrocollagenous tissue, and with a small pore size on the other side to prevent ingrowth and adhesion formation. The patch was implanted in 50 PVG rats with an abdominal wall defect. The patches were harvested after 1 ($n = 5$), 2 ($n = 5$), 4 ($n = 5$), 8 ($n = 5$), 16 ($n = 5$), 32 ($n = 5$), 64 ($n = 5$), 128 ($n = 10$) and 192 ($n = 5$) days. Reherniations and adhesions were scored, stress/strain measurements of the muscle patch interface were performed and the extent of ingrowth on either side of the patch was examined microscopically.

Reherniations were found in six (12 per cent) rats. The breaking strength increased to 8 N cm^{-1} at 64 days, after which it remained constant. Firm adhesions between the omentum and the patch were found during the first 16 days, after which adhesions were found only to the rim of the patch. No bowel adhesions were found. Microscopically, little ingrowth of fibrocollagenous tissue was found on either side of the patch.

It is concluded that this new patch anchors itself firmly to the abdominal wall, but its propensity to induce omental adhesions during the first 16 days is a potential drawback.

Use of Marlex mesh in recurrent incisional hernia repair

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To assess the efficacy of Marlex (C.R. Bard) mesh in the repair of incisional hernia, the records of 98 patients were analysed retrospectively. A total of 102 operations for recurrent incisional hernia was carried out between January 1971 and December 1989. Marlex mesh had been used in 49 cases (group 1) and in the remaining 53 cases a primary closure had been performed using nylon sutures.

There were no postoperative deaths in either group. Four (8 per cent) major complications were noted in group 1 (two wound infections, one respiratory failure, one prolonged ileus) and ten (19 per cent) in group 2 (three wound infections, five respiratory failures, two prolonged ileus), all of which were conservatively managed. The mean hospital stay was 7.0 and 9.2 days in groups 1 and 2 respectively.

One patient from each group was lost to follow-up and the remaining 96 were followed up for 1–15 (mean 7.6) years. There were four patients (8 per cent) in group 1 with a recurrence and 13 (25 per cent) in group 2 ($P < 0.001$). A further surgical repair with Marlex mesh was carried out in four of the 13 patients in group 2. No other patient in either group needed reoperation and all remain symptom-free.

The use of Marlex mesh is a safe and cost-effective procedure. It also has good long-term postoperative results and should always be considered in the management of the complicated problem of a recurrent incisional hernia.

Fascia closure after upper midline laparotomy: results of a randomized trial comparing three absorbable sutures

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A prospective randomized trial was carried out to compare three absorbable sutures, polyglactin 910 (Vicryl), polydioxanone (PDS) and polydioxanone (PDS II) for closure of the abdominal wall after upper midline laparotomy for elective surgery.

The technique was always a continuous closure. The criteria used to assess the results were the occurrence of wound infection and dehiscence in the early postoperative period, and the occurrence of suture sinuses and incisional hernia 1 year after operation.

Early postoperative results in 235 patients revealed no wound infection and no wound dehiscence. A total of 203 patients were reviewed after 1 year. The patients were equally divided over the three trial groups which showed no statistically significant differences for age, sex, risk factors, type of operation or experience of the surgeon. Suture sinuses developed in four patients (2 per cent) 2 months after operation which spontaneously disappeared. The total number of incisional hernias detected 1 year after operation was 22

(11 per cent; PDS 14.2 per cent, Vicryl 11.2 per cent, PDS II 8.4 per cent). The difference between the three groups was not statistically significant.

The results indicate that absorbable sutures have a very low incidence of suture sinuses, and that PDS II seems to be a good choice for closing laparotomy because the incidence of incisional hernia is as low as the incidence described with the use of nylon¹.

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'Expanded polytetrafluoroethylene' darn repair of inguinal hernia

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The aim of the present study was to investigate whether the new surgical techniques and use of well tolerated and lasting sutures reduce the recurrence rate and contribute to the achievement of a good postoperative result.

A total of 116 men of mean age (range) 51.1 (23–71) years underwent unilateral elective inguinal hernia repair, 44 for direct and 72 for indirect inguinal hernias. The Moloney technique (nylon darn) was applied and modified as follows: instead of the nylon suture, a monofilament suture was used, made from expanded polytetrafluoroethylene (ePTFE); in addition, the transversalis fascia repair was reinforced by an ePTFE suture stitched in an interlacing manner after the reinforcement of the internal ring by the same suture. This technique is known as the 'ePTFE darn'. The postoperative course of all patients was free from any severe complications. None of the patients developed symptoms of inguinal nerve entrapment, sinus formation, deep sepsis and discharging haematoma or testicular swelling. There were three (2.6 per cent) superficial wound infections, which healed without complication. The mean postoperative hospitalization was 3.7 days. The ePTFE suture was tolerated well by the tissues in all cases, with no local reaction. No patient required removal of the sutures. The patients were followed up for 5 years after the operation. Recurrence was observed in only two cases (1.1 per cent).

We conclude that the use of an ePTFE suture, which is well tolerated by the tissues, and the reinforcement of the transversalis fascia stitched in an interlacing manner by the same suture, reduce the recurrence rate of inguinal hernia.

Repair of abdominal incisional hernia reinforced by absorbable Dexon mesh prosthesis: 102 cases

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Among 202 postoperative abdominal incisional hernias treated during 8 years, 102 (50.5 per cent) were treated by parietoplasty reinforced by absorbable Dexon mesh placed prefascially. The remaining 100 patients underwent simple parietoplasty for minor defects (less than $5 \times 5 \text{ cm}$ in 79 cases), or replacement by non-absorbable prosthesis in case of major material loss (21 cases).

The patients, 68 women and 34 men, average age 53.6 (range 21–81) years possessed an average of 2.3 of seven risk factors (emaciation, smoking, steroid therapy, repeat surgery etc.). Parietal defects (midline 88; lateral 14; single 76), had an average size of $178 \text{ (range } 28\text{--}650) \text{ cm}^2$.

There were no deaths; the morbidity rate was 3.9 per cent. There were three cases of serious haemorrhage and one delayed sepsis at 3 months related to 21 associated reoperative intra-abdominal procedures.

The mean follow-up is 51.6 (range 0–96) months; 31 patients have been followed and re-examined at 5 or more years, 51 at 4 years, 61 at 3 years; three recurrences (2.9 per cent) have been noted at 2 years.

Temporary internal support by means of an absorbable Dexon mesh prosthesis (placed prefascially) is a reliable and effective technique.

The good long-term results confirm the need for parietal reinforcement during the period of greatest mechanical weakness of the abdominal wall (during the first days). In all, 68 of those operated on had a previous recurrence of the incisional hernia less than 3 months after treatment.

Successful local repair of paracolostomy hernia with a new polypropylene prosthesis

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This study presents the clinical results of implantation of a newly developed prosthetic device for the local treatment of paracolostomy hernia. The prosthesis consists of a polypropylene ring with an internal diameter of 20, 25 or 30 mm, mounted in the centre of a polypropylene mesh. After mobilizing the stomal loop of bowel and tightening of the trephine opening in the abdominal wall, the prosthesis is sutured with polypropylene onto the outer side of the abdominal fascia.

In the period October 1988 to April 1991, 14 patients with symptomatic hernia complicating an end colostomy in the left lower quadrant of the abdominal wall have been treated with this technique by five different surgeons in four hospitals. The mean age of these patients was 56.4 (range 46–77) years. In four patients one or more attempted local repairs had previously been unsuccessful with or without polypropylene mesh or resiting. In 13 patients, postoperative recovery was uneventful. In one patient, however, a wound infection developed, caused by *Staphylococcus aureus*. After a mean follow-up of 18.2 months, no other complication or recurrent hernia has been noted.

The basic event in the aetiology of parastomal herniation is enlargement of the trephine opening due to tangential forces working on the circumference of this opening. This prosthesis seems to neutralize these forces effectively.

Ambulatory surgical treatment under local anaesthesia of primary inguinal and femoral hernia

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The results in terms of patient acceptance, early recurrence rate and economic savings of ambulatory treatment under local anaesthesia of uncomplicated inguinal or femoral hernia are presented.

A retrospective review of 300 consecutive patients operated on by the authors, using a modified Lichtenstein technique, has been made. Follow-up data were obtained by individual questionnaires sent to the patients and their primary physicians. Economic analysis was made using national data regarding mean expenditures in institutions of different sizes.

Patient acceptance of the procedure was excellent. Over 90 per cent of the patients state that the cure has been painless and that they have been able to resume their activities without disability after a few days. Early recurrence rate has been low (<2 per cent), with most of the cases of early recurrence happening early in the experience of the authors. The economic evaluation shows that the procedure brings huge savings, by reducing by almost two-thirds the costs of other conventional methods of cure and by returning patients to normal activity much earlier.

In conclusion, ambulatory treatment under local anaesthesia of primary inguinal and femoral hernia is very well accepted by patients. It is also a viable, sound and very effective alternative for the treatment of this condition in a period of growing budgetary constraints.

Laparoscopic inguinal hernia repair

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Laparoscopic surgery has broadened the surgical therapeutic options for the patient presenting with an inguinal hernia. Over a 15-month period we performed 30 laparoscopic indirect inguinal hernia repairs in 26 patients. Criteria for selection were patients <35 years of age without previous ipsilateral hernia repair. The repair involved formal laparoscopic suturing of the internal inguinal ring. The mean follow-up was 8 (range 1–15) months. Anaesthetic time (AT), postoperative visual analogue pain scale (PS), postoperative hospital stay, morbidity and recurrence were noted.

There was one case of urinary retention after operation. Video review showed that the one case of recurrence was due to fracture of

n	AT (min)	PS	Stay (days)	Morbidity	Recurrence
30	105	1.7	1.6	1	1

a Prolene suture traumatized during the repair. These results indicate that laparoscopic management of inguinal hernias is feasible. However, while these early results are encouraging, a stringent clinical trial and long-term follow-up will be necessary before the role of this new surgical procedure is validated.

Transabdominal laparoscopic inguinal hernia repair by preperitoneal prosthetic mesh

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Several new procedures of laparoscopic hernia repair have been investigated. Among these the most popular include the placement of prosthetic mesh (polypropylene), either rolled into the inguinal canal or fixed on the inguinal ring like a patch or plug. Simple closure of the inguinal ring has also been tried, as well as placement of preperitoneal mesh by either transperitoneal or extraperitoneal approaches. This latter procedure alone has become standard as an open technique, with reliable results.

Five male patients with direct (two) or indirect (three) hernias of the groin underwent laparoscopic repair under general anaesthesia. After creation of pneumoperitoneum, three trocars were introduced (umbilical 10 mm, iliac fossa 5 and 11 mm). The peritoneum was dissected with a reversed U shaped incision, surrounding both internal and external inguinal rings. The peritoneal flap and its postinferior hinge were dissected from the preperitoneal space and from the contents (inferior epigastric vessels, spermatic vessels and vas deferens), ensuring treatment of the sac without ligation. A polypropylene mesh was applied to the hernial defect, allowing overlap of cord structures and abdominal wall. The mesh was secured in place by interrupted stitches. The peritoneum was then closed by continuous sutures. Urinary and gastric catheters were removed on the same day.

The mean operating time was 2 (range 1.5–3) h. In one case the laparoscopic procedure was abandoned because of obesity. For the four other patients, pain was minimal (three) or moderate (one). The postoperative stay was <48 h. No mortality, morbidity or recurrence occurred.

In conclusion, the decrease in postoperative pain and early return to full activity are the major advantages of this procedure, which allows cover of all internal weak points in the groin. The transabdominal laparoscopic approach is technically easier than that of the laparoscopic preperitoneal method. Furthermore, complete exploration of the abdominal cavity is always possible. This procedure appears more efficient than simple closure of the inguinal canal or inguinal ring, but the method requires further study.

Multifilament versus monofilament absorbable sutures for abdominal closure

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The aim of the study was to compare the frequency of wound dehiscence, herniation and time of suturing for a monofilament, absorbable, continuous suture (MAC) with a multifilament, absorbable, interrupted suture (MAI).

Before closure of an abdominal incision, 1013 patients were randomized to either MAC (O-Maxon; Davis and Geck) or MAI (O-Vicryl; Ethicon). The patients were examined 1 year after the operation for wound herniation, suture granulomas and other wound complications.

Of the original group 709 patients (70 per cent) were available for follow-up 1 year after the operation. A total of 179 (18 per cent) had died and 125 (12 per cent) did not attend follow-up. The two groups were comparable with regard to age, sex, height, weight, preoperative haemoglobin, types and length of the incisions, infection and

other co-morbidity, diagnoses and operative procedures. Herniation occurred in 8 per cent of the patients in the MAC group compared with 6 per cent in the MAI group (P not significant). Wound dehiscence occurred in 1 per cent in both groups. The mean time for suturing was 7 min in the MAC group and 9 min in the MAI group ($P < 0.001$).

Closure of an abdominal incision with a monofilament absorbable continuous suture is as safe as, and faster than, a multifilament absorbable interrupted suture.

Polypropylene mesh hernioplasty: a single technique for inguinal and femoral hernias

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Preliminary results are presented of a single polypropylene mesh hernioplasty technique for groin hernias.

Under local or regional anaesthesia, the inguinal canal was opened and the hernia identified. Indirect sacs were opened, explored and excised. Direct sacs were inverted by means of a single, absorbable, invaginating suture. A femoral sac was converted to an inguinal one. Dissection of the posterior wall of the inguinal canal revealed the inguinal ligament, the lacunar ligament, the femoral sheath and Cooper's ligament. A sheet of prosthetic mesh measuring about 7×10 cm was fashioned. Line A of the mesh was anchored to Cooper's ligament by four or five interrupted sutures, the medial sutures fastening the mesh to the lacunar ligament. Line B was fixed to the femoral sheath with two or three interrupted sutures. The mesh was turned and projected against the posterior wall of the inguinal canal and line C was anchored by a running suture along the inguinal ligament 2 or 3 cm beyond the internal ring. A slit was made in the mesh at the internal ring to allow the spermatic cord to emerge and the external part of the cut was closed by interrupted sutures. The superior edge of the mesh was fashioned to the anatomy and secured by a similar, continuous suture to the rectus sheath and conjoint muscle and tendon above. The external oblique aponeurosis was closed over the cord with a continuous absorbable suture.

Since January 1990, 43 patients with direct, large indirect and femoral hernias (primary or recurrent) have been operated on using this technique. No infection has occurred. There have been three haematomas which resolved spontaneously. To date there have been no recurrences.

This appears to be a promising technique because it is a safe and simple approach for the simultaneous treatment of inguinal and femoral hernias.

Right inguinal hernia following appendicectomy

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The possible effect of appendicectomy on the subsequent development of right inguinal hernia was investigated in 583 patients. The data were recorded prospectively in 510 cases while the records of 74

patients were retrospectively analysed; 73 of the latter group were included in the study. The patients were subdivided according to whether they had undergone appendicectomy. A total of 42 patients with inguinal hernias had incisions in the right lower quadrant, 40 of which were classic McBurney. Of the 42 patients who had undergone appendicectomy 28 (67 per cent) developed right inguinal hernias compared with 295 (55 per cent) of the 541 patients who had not. The right:left ratio in the groups was 2.1:1 and 1.5:1, respectively ($P > 0.3$). There was no significant difference in the incidence of right-sided hernias between the two groups. Neither sex was more prone to develop an inguinal hernia after appendicectomy, and no type of hernia (direct or indirect) predominated. The cause of the right-sided inguinal hernia after appendicectomy has been ascribed to the damage of the nerves that innervate the inguinal region. The incisions in most of our cases were some distance away from the most common areas of nerve damage as depicted by the anatomical charts of the nerve routes.

In conclusion, the development of a right inguinal hernia is an unlikely complication of appendicectomy if a classic McBurney incision is used.

Major ambulatory general surgery

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The aim of this study was to demonstrate the usefulness of a major ambulatory general surgical unit. In the period from October 1990 to November 1991, 141 general surgical procedures and 698 specialty surgical procedures were performed in the unit. Inclusion criteria were patient agreement to ambulatory surgery, social and family status, and absence of major medical illnesses. General surgical procedures were inguinal, umbilical and epigastric hernia in 67 patients, pilonidal cyst in 29, anal surgery in 24, and large cutaneous and subcutaneous lesions in 21 patients. Anaesthetic techniques were general in 16 per cent, regional in 48 per cent, and local in 35 per cent of patients.

Of 141 patients, 11 (8 per cent) could not be discharged immediately after surgery as a result of unsatisfactory anaesthetic recovery, unexpected complexity of the procedure and severe pain. Postoperative follow-up was by telephone in all patients, and by home visit by a trained nurse in 85 per cent of patients. Three patients were readmitted because of bleeding (pilonidal cyst), abscess (herniorrhaphy) and headache (epidural anaesthesia). Of all patients, 96 per cent were satisfied with the result of ambulatory surgery. As a direct result of the activity in the unit of ambulatory surgery, waiting lists for patients needing procedures usually performed under hospital admittance were substantially reduced.

Significant reductions in waiting lists for elective surgery and more effective use of surgical areas without an increase in postoperative complication rate demonstrate the usefulness of a major ambulatory surgical unit.

Hydatid disease

Selecting the best treatment for hepatic hydatidosis

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Hydatidosis is still endemic in Mediterranean countries, particularly in the south of Italy, the liver being the main organ affected.

In the past 12 years, 100 patients underwent operation for liver hydatid disease in this surgical department. The male to female ratio was 1:27:1 and the median age 46 years. Eighteen patients were treated with hepatic resection, 30 had a total and 24 a subtotal cystopericystectomy, while the remaining 28 cases underwent capitonnage. In six cases a multiorgan resection was performed because of other localizations of the parasite: in the spleen (one), lung (two), kidney (one), retroperitoneum (one), and rib (one). In 11 cases there were multiple localizations in the liver. Three postoperative deaths occurred in our series due to sepsis, respiratory failure and haemorrhage (in a patient with cirrhosis). Twenty-five major complications were seen (five biliary fistulae, seven haemorrhages, one sepsis, one hemiplegia, one subphrenic and two intraperitoneal abscesses, one pneumothorax, one respiratory failure, and six cases of pleuritis) and there were 28 minor complications. Complication rates after total or subtotal cystopericystectomy and hepatic resection were similar (26.6 per cent, 29 per cent and 28 per cent respectively), while there were five major complications (18 per cent) after capitonnage. No recurrences occurred after the major operations, while three were recorded in the capitonnage group.

Although liver hydatid disease is a benign condition, its treatment is still affected by a high complication rate and even mortality. Therefore, since the main goal of the treatment of liver hydatidosis is the eradication of the parasite with minimum surgical risk, subtotal cystopericystectomy seems to be a safer form of treatment than total cystopericystectomy. Hepatic resection should be reserved only for very selected cases with large cysts involving an entire hepatic lobe or the vascular pedicle of a lobe or segment.

Surgical treatment of pericyst in liver hydatid cysts

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This is a retrospective analysis of the results of treatment of pericysts in liver hydatid cysts. The group studied consisted of 94 patients, 56 men and 38 women, age range 21–68 years. Patients were submitted to specific tests. Multiple cysts were found in 11 patients. The most frequent location was the lower right lobe ($n = 79$). The volume of the cysts varied between 21 and 100 ml. All cysts were resected. When the cyst destroyed the majority of an anatomical territory, particularly in the left lobe, partial hepatectomy was performed ($n = 12$). As subtotal pericystectomy ($n = 2$) presented a vascular risk, in cases where the hepatic tissue was normal simple resection of the cyst dome ($n = 9$) was performed, sometimes completed with partial resection of the pericyst ($n = 65$). For cysts with thickened walls on the lower surface of the liver, pericystodigestive anastomoses were made between the wall of the residual cavity and a Roux loop of small intestine ($n = 3$) with the duodenum ($n = 2$) or with the stomach ($n = 11$). Combined lesions of the biliary tract made it necessary to perform nine cholecystectomies and 16 Kehr drainages. In most cases drainage of the residual cavity was ensured by at least two drainage tubes of large diameter. For the others ($n = 8$) external drainage and transperitoneal drainage was necessary. Postoperative complications and hospital stay differed depending on the anatomical aspect of the cyst. Biliary stasis ($n = 10$), suppuration of the residual cavity ($n = 11$) and subphrenic abscess ($n = 1$) were noted. Only one patient died of pulmonary embolism. Recurrences appeared after 6 years in two patients. Resection of the cyst dome complete with limited resection of the pericyst is an operation without major risk in liver hydatid cysts. This is well adapted to the existing conditions in our country.

Hydatid cyst–bile duct intrahepatic communication: surgical strategy

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The incidence of communications between liver hydatid cysts and intrahepatic bile ducts is not known and published data differ, but nevertheless, such communications demand a change of surgical strategy. Of 386 consecutive patients undergoing operation for liver hydatid disease, this study documented communications in 90 (24.5 per cent). The median age of the patients was 39.9 years, and the median cyst diameter was 10 (range 5.5–20) cm. Solitary cysts were found in 76.4 per cent of patients and the right lobe was involved in 68.1 per cent. Where there was a large opening within the cyst, the bile ducts were visualized (by intraoperative catheter cholangiography and ultrasonography) and the level of the communication assessed.

Suture was feasible in 73 patients (81 per cent; minor, peripheral ducts), suture combined with T tube drainage and choledochoduodenostomy in ten patients (11 per cent), while seven patients (8 per cent) had a T tube drainage only. The median postoperative hospital stay was 24.7 (range 7–93) days. The most frequent complication was wound infection (21 patients; 23 per cent), pleural effusion (13 patients; 14 per cent) and biliary fistula (seven patients; 8 per cent).

The main cause of prolonged hospital stay was infection and wound drainage. Biliary fistulae closed spontaneously in four patients but endoscopic sphincterotomy was necessary in the remaining three patients. We conclude that hydatid cyst–bile duct communications are frequent and should be searched for during operation regardless of the colour of the cyst contents. Communications are usually peripheral and involve small ducts that can be sutured safely. Prolonged hospital stay is due to a high incidence of infected cyst contents and resulting postoperative infection. Long-term results are good, conservative management spares liver tissue and postoperative bile duct fistulae can be managed without operation.

Trace elements in hydatid disease

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Serum and hydatid cyst fluid levels of selenium, zinc and copper were investigated in patients and in sheep with hydatid cysts using atomic absorption spectrophotometry (Varian Model 30/40). Results were compared with those of healthy subjects in both species.

Serum levels of selenium and zinc were lower in both humans and sheep with hydatid disease, while the serum copper level was found to be raised ($P < 0.001$). Similarly low selenium and zinc levels have been reported in patients with cirrhosis, cancer and rheumatoid arthritis. Furthermore, low serum zinc levels have been cited in various infectious diseases. These results suggest that hydatidosis should be considered among the group of diseases causing low serum selenium and zinc levels. The elevation of copper compares with other studies in which high serum copper levels have been reported in hepatic cancer. We therefore believe that the diagnosis of hydatidosis should be considered in cases with high serum copper values. Selenium was absent in cyst fluid while copper and zinc levels were significantly lower than in serum. Copper and zinc levels in cyst fluid were similar in both species.

Clinical features of complicated hydatid cysts of the liver

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One hundred cases of hepatic hydatid cysts (HHC) with acute complications were studied. This is a retrospective study of the cases operated on between 1982 and 1991, with emphasis on clinical presentation and therapy. All the cases were operated on 6–72 h after

admission. The clinical features were of hepatobiliary symptoms (56), acute cholecystitis (26), cholangitis with jaundice (26) and cholecystitis and pancreatitis (four). Peritoneal symptoms were seen in 16 cases, either due to generalized peritonitis (12) or to subphrenic abscess (four). Preoperative diagnosis of HHC was possible in only 26 cases. Septic and perforating complications made drainage the main therapy. This consisted of the simple drainage of the secondarily infected cystic cavity (17) or partial pericystectomy (67). Radical surgery was rarely necessary and consisted of cystectomy (11) and hepatic resection (six). There were 18 cholecystostomies, 27 external biliary drainages and 41 cholecystectomies. Abscess of the residual cavity (13) was the most frequent complication, together with intermittent cholangitis (11). Ten deaths occurred. HHC may mimic perforated ulcer, generalized peritonitis, subphrenic abscess, cholangitis and acute cholecystitis. The main therapeutic aim is the resolution of the septic complication and secondarily, removal of the lesion.

Treatment of hydatid cysts of the liver by a pericystointestinal anastomosis

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In the past decade, several authors have reported good results in treating hepatic hydatid cysts by a pericystointestinal anastomosis using mainly small intestine, stomach or duodenum.

In the present study, 282 cases of hydatid cyst of the liver were reviewed over a period of 25 years, between 1964 and 1990. After aspiration of the cystic cavity and removal of the entire hydatid membrane, a hypertonic solution was used to sterilize the residual cavity. In 53 cases (19 per cent), a pericystointestinal anastomosis was performed using either the stomach (14 cases, 5 per cent) or the small intestine (39 cases, 14 per cent). The alternative procedure was a laterolateral Roux-en-Y pericystojejunal anastomosis. All patients had a favourable postoperative course. No leakage or haemorrhage occurred. Ultrasonographic and radiographic follow-up of the residual cavity showed a rapid decrease within 30–45 days.

The Roux-en-Y pericystojejunal anastomosis is a good alternative for treatment of a hydatid cyst localized on the inferior surface of the liver. The pericystic wall must be suitable for a good suture and should not be calcified, and the cavity should be large enough for a laterolateral anastomosis.

Complicated hydatid cysts of the liver

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Of 437 patients with hepatic hydatid cysts undergoing operation between 1950 and 1990, 188 (43 per cent) presented with 207 complications (suppuration in 60 patients, perforation into the biliary tract in 72, into the peritoneum in 38, into the lung and pleural cavity in 12, and into the duodenum in one, and cyst calcification in 24). The incidence of complicated cysts was reduced by early ultrasonographic diagnosis. Intrahepatic ruptures were manifested by cholangitis in 29 patients, obstructive jaundice in 19, associated gallstones in nine, sclerosing hepatitis in three and cholangiosclerosis in one. Rupture of the cysts into the peritoneum presented as hydatidoperitoneum, secondary echinococcosis of the peritoneum or primary heterotopic echinococcosis. Surgical treatment evolved in stages. In biliary complications, we favoured a surgical approach with external and internal drainage, associated cholecystectomy, adventitial resections and plastic procedures to the cavity. Ruptures of the cysts into the peritoneum have necessitated emergency surgery, and repeated laparotomy has usually been necessary. Rupture into the pleural cavity and biliary-bronchial fistula necessitate an abdominal and thoracic approach and sometimes lung resection (as in one case in the present series). The mortality rate in this series was 2.8 per cent. The main postoperative problems were prolonged biliary drainage and a slow reduction in the cavity.

Surgical treatment of hydatid disease of the liver

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The effectiveness of the more conservative surgical methods in the treatment of hydatid disease of the liver was studied. A total of 43 patients with hydatid disease of the liver was treated from June 1987 to May 1991. There were 28 women and 15 men. The mean age was 45.3 years. In eight cases (19 per cent) there was a history of a previous operation for hydatid disease. The main symptoms were: pain in 29 patients (67 per cent), abdominal mass in nine patients (21 per cent), obstructive jaundice in three patients (7 per cent), fever in one patient (2 per cent) and itching in one patient (2 per cent). Ultrasonographic examination was in 36 cases (84 per cent) the primary means of diagnosis but computed tomography was used routinely to define the localization(s) and extension(s) of the cyst(s). The total number of cysts was 60. The treatment methods used were: external drainage (40 cysts; 67 per cent), total excision (eight cysts; 13 per cent), inflexion (seven cysts; 12 per cent), hepatic resection (two cysts; 3 per cent) and omentoplasty (three cysts; 5 per cent). In two cases there were cystopleural fistulae requiring thoracotomy and thoracic drainage as a part of the primary operation. Three cysts had major biliary communications and two of them necessitated T tube drainage of the common bile duct and the remaining case needed sphincterotomy and sphincteroplasty. The mean (range) postoperative hospital stay was 12.5 (8–27) days. One patient had an abscess in the cyst cavity which required reoperation and drainage. External biliary fistulae occurred in three patients and they closed spontaneously in 22 to 35 days. The morbidity rate was 9 per cent (four of 43). There was no mortality.

From our experience and from these data we conclude that conservative surgical methods in the treatment of hydatid disease of the liver are as effective as the more aggressive surgical methods proposed in the world literature.

Significance of intracystic pressure in intra-abdominal hydatid cysts

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A prospective study has been performed on 32 patients with 50 intra-abdominal hydatid cysts. The significance of intracystic pressure (ICP) to predict cyst viability has been investigated. Forty of the cysts were in the liver (80 per cent), two in the spleen (4 per cent) and eight elsewhere in the abdomen (16 per cent).

ICP was measured during operation from the apex of the cyst with the aid of an 18 Fr needle connected to a water manometer. The diameter, location, the unilocular or multilocular nature, and the characteristics of the intracystic fluid were also noted.

Of the 40 cysts located in the liver, 31 were viable and nine were non-viable. The mean ICP was 36.9 cmH₂O in viable cysts and 0.3 cmH₂O in non-viable cysts ($P < 0.01$). The mean pressure in cysts located in the right lobe of liver was 24.7 cmH₂O, while the mean pressure in cysts of the left lobe was significantly higher at 50.4 cmH₂O ($P < 0.001$). The mean ICP in 14 univesicular (37.6 cmH₂O) did not differ from that in the 17 multivesicular hepatic cysts (36.3 cmH₂O).

In conclusion, it has been found that intraoperative measurement of ICP is a simple and reliable method for assessment of the viability of hydatid cysts. Low ICP indicates non-viability, while high ICP predicts viability.

Postoperative biliary complications of hydatid disease of the liver and their treatment

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In this study different methods of management of postoperative biliary complications of hepatic hydatid disease are compared. Between 1985 and 1990, 393 of 548 patients with hydatid disease were operated on because of hepatic infestation. Postoperative bile fistulae

Hydatid disease

occurred in 22 cases, and cholangitis in two cases. Thirteen patients underwent a surgical procedure and endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) performed in eight cases. Spontaneous closure of the fistula occurred in the other three cases. The interval between ES and closure of the external bile fistula ranged from 3 to 15 (mean 7) days, and that between the surgical procedure and closure of the fistula from 7 to 50 (mean 19) days. Both patients with cholangitis experienced relief of their symptoms immediately after ES. Compared with surgery, ES offers a less aggressive approach and a shorter interval to closure of bile fistula ($P < 0.05$).

In conclusion, ERCP with ES is an effective mode of treatment of postoperative biliary complications of hepatic hydatid disease, which is preferable to further surgery.

Management of the residual cavity in surgical treatment of hepatic hydatid cyst

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This study is a retrospective analysis of 80 patients operated on for hepatic hydatid cyst. The surgical treatment depended on the topographical location of the cyst, its volume and the presence or absence of complications. Ideally, cyst resection was performed in cases of surface uncomplicated cysts. Cystotomy with partial pericystectomy followed by tunnelling and draining of the remaining cavity was the technique adopted for cysts located deeply and/or located on the bile ducts. Cystotomy with cavity cleaning and draining was the surgical treatment in cases of suppurating cysts. Cystogastrostomy was performed in large cysts externally located on the lower side of the left lobe. Cholecystectomy was performed during the same operation, either for associated lesions or for technical reasons. Cholelethotomy and Kehr-type external drainage of the main bile duct were performed where the cyst cavity communicated with intrahepatic bile ducts or where the main bile ducts showed signs of hydatid mechanical obstruction. The postoperative course varied, depending on the management of the remaining cavity. Thus, after cystectomy, cyst resection or cystogastrostomy, the mean healing time was 1 month. After partial pericystectomy with tunnelling and draining of the remaining cavity, the mean postoperative recovery time was 60 days. There were no deaths in this series of 80 patients. Excision of hepatic cysts, if feasible, expedites recovery.

Dynamics of residual cavity after hepatic hydatid cyst surgery

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The ultrasonographic study of residual cavity evolution after hepatic hydatid cyst surgery is reported. Ninety patients operated on for hepatic hydatid cyst were investigated. Of these, 26 who had preoperative ultrasonography were followed up by ultrasonographic monitoring at 1, 3, 6 and 12 months after operation. A group of 64 patients operated on 1–10 years previously was investigated by ultrasonography, the correlation between ultrasonographic images and surgical findings being established retrospectively. No ultrasonographic changes were found in patients operated on by ideal cystectomy or hepatectomy. In cases treated by reduction without drainage, large residual cavities are constantly present, so that late after operation the ultrasonographic differential diagnosis from hepatic hydatid cyst recurrence is sometimes difficult. In prospectively studied patients with Mabitt–Lagrot pericystectomy (15 cases), the ultrasonographic patterns are directly related to the hepatic hydatid cyst topography and delineation which influence the surgical approach and drainage, and not to the preoperative cyst complications. During the first month after surgery the residual cavity is practically present in all cases. In all of these 15 patients, the residual cavity progressively reduced, but it completely disappeared after 12 months in only five. In patients with healed lesions incidentally investigated, some ultrasonographic patterns were seen: constant residual cavity, or pseudotumoral images (omentoplasty) or linear echogenic scar or absence of any pathological change. The topography and delineation of the hepatic hydatid cyst, the surgical technique and the amount of initial pericystectomy are the factors that determine the reduction of the residual cavity.

Treatment of hydatid hepatic cysts

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One hundred and seventeen patients with hydatid hepatic cyst underwent surgical treatment between January 1980 and December 1990. The treatment of the residual cavity varied according to the position, number, size, state of cyst and the general state of the patient. The procedures used for simple cysts were: ideal pericystectomy (nine cases), spread pericystectomy (79 cases) and partial pericystectomy (13 cases), with aspiration drainage of the remaining cavity. In complicated cysts, bipolar drainage was used (24 cases) without separating the biliary fistula from the remaining cavity by cystobiliary deconnection. In large multiple hepatic cysts the following types of partial hepatectomy were performed: right lobectomy (three cases), left lobectomy (five cases), right lateral segmentectomy (one case) and left lateral segmentectomy (four cases). Atypical hepatectomy was performed in three cases, though it remains an uncommon procedure in the treatment of hydatid hepatic cyst. Ideal pericystectomy resulted in the shortest hospital stay (mean 3 weeks). Mortality and morbidity rates are less than with bipolar drainage which results in a mean hospital stay of 5 weeks.

Hydatid cysts of the liver in children

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This study reports 249 cases of hydatid cysts of the liver (HCL) in children, studied over a period of 10 years. This series of cases is one of the largest yet published and represents the total seen in paediatric surgery clinics and the principal paediatric surgery departments throughout Romania.

There have been increasing numbers of cases in some regions in our country and a higher proportion among women and cases from rural areas.

The disease is frequently met in children under school age and in schoolchildren. Ten cases were observed in children 1–3 years of age. This contradicts theories which state a longer time interval is necessary for the appearance of large HCL.

Investigations consisted of radiological examinations, IDR Cassoni, echography and scintigraphy of the liver. We found that the clinical diagnosis was usually correct. The sites of the HCL are described. Special note was taken of secondary infection with *Echinococcus*. We emphasize the surgical treatment in different types of cysts (lateral, paramedian, infradiaphragmatic), or in multiple HCL, and also in HCL appearing in various visceral sites. Postoperative complications are reported. The postoperative results are good with zero mortality. This is a success story for paediatric surgery in Romania.

Risk factors in hepatic hydatid disease

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Analysis of 417 patients between 1979 and 1990 outlined the presence of some risk factors in the treatment of hepatic hydatid disease. The following factors were studied: (1) location near the vasculobiliary pedicles and the adjoining organs limiting surgical intervention to reduced pericystectomy (27.5 per cent of patients); (2) size of the cyst (diameter >20 cm; 37 cases); (3) multiplicity of the cysts (30.4 per cent); (4) recurrent cysts (12.7 per cent); (5) suppurating cysts (19.1 per cent); (6) obstruction of the main biliary duct by hydatid material with or without jaundice (12.2 per cent of the cases – 74.4 per cent of those with jaundice had ascending cholangitis). There were also secondary risk factors: rupture of the hydatid cyst into the peritoneum (four patients); external fistula (three cases) and cystopleural or cystobronchial fistula (seven patients). The above cases had intraoperative technical difficulties but partial pericystectomy operations predominated (89.2 per cent). Only 10.8 per cent of the patients had the advantage of more complete interventions such as pericystectomy, total pericystectomy or hepatectomy.

Therefore, as a result of the risk factors mentioned, in most cases the surgery performed was unsatisfactory. The general postoperative mortality rate was 5.4 per cent and the postoperative morbidity rate was 24.3 per cent.

As a result of the many risk factors, hepatic hydatid cysts, although benign, may pursue a 'malignant' course.

Common bile duct obstruction in hydatid cyst of the liver: surgical management

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This paper reviews the surgical policy of common bile duct obstructions of hydatid aetiology.

Since 1971, 72 patients have undergone operations for hepatic hydatid disease. Obstruction was secondary to hydatid elements in the distal common bile duct in 52 patients, due to papillary stenosis in 12, and to both mechanisms in eight. There were two stages to the operation. After evacuation of the hydatid cyst, the large cystobiliary communications were closed with fine sutures or, in selected cases, by suturing a pedicle of omentum within the residual cavity. The cyst cavity was treated by external drainage or partial cystectomy. Then a choledochotomy was performed, the hydatid elements were removed from the biliary tract and the sphincter was carefully explored. If no duct stenosis was found (40 patients), or when the papillary lesions appeared to be reversible (four patients), T tube drainage was performed. In the second group of 28 patients, the following surgical procedures were used. In the presence of papillary stenosis with moderate duct dilatation, sphincterotomy was performed (16 patients). In those patients in whom the biliary tree may not have been completely cleared, particularly if there was a large biliary fistula (six patients), or if the bile duct was dilated above 20 mm (six patients), then a choledochoduodenostomy was performed. Three patients died after operation from septic shock (4 per cent) and another two required reoperation for stenosing cholangitis after the use of formalin (Roux-en-Y hepaticojejunostomy).

It is concluded that the main goals of surgical treatment are to eliminate the source of obstructing hydatid elements and allergy and then to treat the common bile duct obstruction by an appropriate method.

Recurrence and multiplicity of hepatic hydatid cysts

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Recurrence and multiplicity of hydatid hepatic cysts are additive risk factors. A total of 417 patients with hepatic hydatid cysts was studied from 1979 to 1990; 53 (12.7 per cent) were recurrent and 127 (30.4 per cent) multiple. These circumstances led to a higher postoperative morbidity rate than single or primary cysts (33.8 versus 24.3 per cent) and an increase in the postoperative mortality rate (5.5–6.2 per cent). Postoperative recurrence suggests a previous unsatisfactory surgical intervention. Recurrence may be: (a) real by reinfestation; (b) false resulting from inadequate intervention, intraoperative insemination or non-discovery by an insufficient search; or exogenous vesiculation on the remaining adventitia and the impossibility of identification of other cyst ducts owing to small dimensions or central hepatic position. The coexistence of multiple and recurrent cysts (19 patients) may result in recurrences by: multiplicity (53), different hepatic topography (69) and undiscovered communicating cysts (73). The optimal methods for prophylaxis of recurrences are: preoperative and

intraoperative complete exploration, extension of the pericystectomy, and radiological and instrumental exploration of the main biliary ducts to find central hepatic lesions.

Multiple and recurrent hepatic hydatid cysts make surgery more difficult and may result in successive reinterventions and possible complications such as cirrhosis or serious intrahepatic septic collections, as occurred in 12 of our cases.

Biliary complications of hepatic hydatid cyst

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A group of 110 patients affected with hepatic hydatid cyst was studied. There were 69 (62.7 per cent) complicated cases, with 76 per cent biliary/hepatic cysts.

The main biliary complications fell into three groups: cystobiliary communication; compression of the hydatid cyst or the biliary ducts; and other complications.

Cystobiliary communications were present in 32 per cent of the patients with hepatic cysts. Cystobiliary fistulae proper appeared in a third of the cases affected by cystobiliary communications. With two patients, the cause of obstructive fistula was compression by hepatic cysts of external biliary ducts.

Other complications comprised nine cases of biliary dyskinesia, three of parahydatid acalculous cholecystitis and three of stenosis of the papilla of Oddi.

Management of liver hydatid disease

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A consecutive series of 469 patients operated on for liver hydatid was analysed. There were 206 men (43.9 per cent) and 263 women (56.1 per cent) with median age 42 (range 12–80) years. The right lobe was affected in 304 patients (64.8 per cent), the left in 60 patients (12.8 per cent), both lobes in 69 patients (14.7 per cent) and 33 patients (7.0 per cent) had liver hydatid and cysts in other organs as well. One patient had disseminated intra-abdominal hydatid. Hydatid cyst–intrahepatic bile duct communications were seen in 104 patients (22.2 per cent). The median duration of hospital stay was 24.5 days.

The majority of patients (229) had partial cystectomy and capitonnage, 119 patients had partial cystectomy and omentoplasty, and 42 patients had total cystectomy. There were only 28 liver resections (typical and atypical). The other patients underwent a combination of procedures. In 41 patients extrahepatic operations were performed during the initial operation for liver cyst. There were nine (1.9 per cent) postoperative deaths. Reoperation was necessary in 20 patients (4.3 per cent). A total of 154 patients (32.8 per cent) had postoperative complications; these ranged from a short-term fever or wound infection (66 patients; 14.1 per cent), pleural effusion (39 patients; 8.3 per cent), biliary leaks in 25 patients (5.3 per cent), to subphrenic collection in 12 patients (2.6 per cent) and others. The majority of complications were in patients presenting with infected cysts.

The authors conclude that liver-sparing surgery gives good results, that liver resection should be reserved for special cases and that the postoperative mortality and morbidity rates are acceptable. Patients did well on follow-up and the recurrence rate is low.

Administration of tumour necrosis factor (TNF) inhibitors after exposure to TNF prevents development of maximal biological effect: an argument for clinical treatment with TNF inhibitors

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The cytokine tumour necrosis factor (TNF) is involved in the pathophysiology of a wide variety of diseases. Pretreatment with anti-TNF antibodies has confirmed its success in animal models of disease. However, whether intervention with anti-TNF antibodies might be useful in the clinical situation in which TNF is already produced is still not known. We therefore studied the relationship between the duration of TNF-TNF receptor interaction and the extent of the induced biological effects in two different systems *in vitro*: (1) the slowly induced cytotoxicity of the TNF-sensitive murine cell line L929; (2) the rapid TNF-induced expression of an adhesion molecule for granulocytes, ELAM-1, on human endothelial cells.

The TNF-TNF receptor interaction was interrupted at different times after onset of stimulation, either by washing away TNF, or by adding TNF activity-blocking monoclonal antibody. To establish an optimal effect for both TNF-induced cytotoxicity on L929 cells and TNF-induced expression of ELAM-1 on human endothelial cells, the TNF receptor had to be occupied by TNF for at least 30–60 per cent of the full incubation period. This observation provides an argument that clinical intervention with TNF inhibitors can be an advantage, even in a situation in which TNF has already been released into the circulation.

Next, we obtained evidence in a clinical study that it is possible to affect the course of TNF-mediated disease by administration of TNF inhibitors. Time-course measurements of plasma interleukin 6 (IL-6) concentrations were performed in patients with septic shock who were treated with anti-TNF antibodies. In an animal model of septic shock, we have shown that pretreatment with anti-TNF antibodies prevents LPS-induced IL-6 release. In patients with septic shock, plasma IL-6 was also influenced by anti-TNF treatment, as plasma IL-6 concentration declined promptly in four of six patients after administration of anti-TNF. We therefore conclude that further clinical research to study the therapeutic effects of administration of TNF-inhibiting agents to patients is justified.

Effect of repeated endotoxin infusion on the production of superoxide and leukotriene B₄ of polymorphonuclear leucocytes

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Sepsis (endotoxaemia) after surgery or trauma often results in adult respiratory distress syndrome (ARDS) and multiple organ failure. Polymorphonuclear leucocytes (PMN) are thought to be responsible for damage to endothelial cells (ECs), which is one of the first steps in ARDS. Leukotriene B₄ (LTB₄) enhances the adhesion of PMN on ECs and oxidative burst products (O₂⁻) disturb the cytoplasmic membrane of ECs.

We have investigated (1) the course of LTB₄ and O₂⁻ production under the influence of repeated infusions of endotoxin (WO111:B4) in pigs ($n = 5$), and (2) the activity of human PMN ($n = 3$) at different times of action of endotoxin.

Before and after each of two infusions, PMN were isolated with Ficoll-Paque centrifugation. The cells were activated with *N*-formyl-methionine-leucine-phenylalanine (FMLP). Human PMN were isolated from healthy donors, incubated with endotoxin for 30 and 60 min and activated with FMLP and PMN. O₂⁻ was measured using the cytochrome-*c* test. The LTB₄ levels were quantified with high pressure liquid chromatography after activating the PMN with calcium ionophore.

PMN activity increased after the first infusion of endotoxin and after 30 min action. With advanced infusions of endotoxin and

advanced time of action of endotoxin the production of LTB₄ and O₂⁻ decreased significantly ($P < 0.05$). This may have resulted from a decrease in FMLP receptors, because PMN activation also increased O₂⁻ production after 60 min incubation with endotoxin.

We conclude that in prolonged or repeated endotoxaemia PMN are not solely responsible for EC damage. It is not surprising that therapy that focuses on blocking PMN function to prevent ARDS during sepsis is not successful. Furthermore, the finding of a reduction in PMN activity after prolonged endotoxin action might explain why bacteraemia is a secondary phenomenon of endotoxaemia, as indicated by recent studies.

Bacterial translocation and endotoxin absorption in organ donors

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The mucosa of the gastrointestinal (GI) tract provides an effective barrier to the entry of bacteria and endotoxins. As shown in animal experiments, this barrier function can be lost in critical illness and thus may lead to translocation of bacteria and absorption of endotoxins. As hardly any information is present about these phenomena in humans without pre-existing GI tract disease, we undertook a prospective study in organ donors because they are at risk of bacterial translocation and endotoxin absorption.

Twenty-one organ donors of mean age 26 (range 3–58) years entered the study. Before surgery a blood sample was taken from the peripheral blood for culture and for measurement of endotoxin level and endotoxin-inactivating activity (EIA). After laparotomy a sample of abdominal fluid was taken for culture and endotoxin level measurement. Subsequently, mesenteric lymph nodes (MLN) were sampled for culture. Before starting organ perfusion a blood sample was taken from the portal vein for culture and measurement of endotoxin level and EIA. After removal of the organs, biopsies were taken from the lung, spleen and liver for culture, and from the jejunum, the ileum and the caecum for histological examination and culture. Cultures were positive if $>10^2$ colony-forming units per gram tissue or >10 colony-forming units per millilitre fluid were isolated.

Positive results were obtained from cultures of the MLN of 11 donors, the lung of seven, the liver of two, the spleen of five and the peripheral blood of one donor. All portal blood and peritoneal fluid cultures were negative. On three occasions, only Gram-negative bacteria were isolated; on 19 occasions only Gram-positive were isolated, and on four occasions both were isolated. All but five of the isolated strains were isolated also from the small bowel. Plasma endotoxin levels >5 pg ml⁻¹ were found in the peripheral blood in donors, in the portal blood in two and in peritoneal fluid in nine of 17 donors. The mean (s.d.) EIA in both peripheral (2.25(2.9) µg ml⁻¹) and portal blood (1.94(2.6) µg ml⁻¹) were significantly ($P < 0.0001$) lower than in a reference group of healthy individuals (8(1) µg ml⁻¹). No mucosal damage was found in the biopsies.

Bacterial translocation is a common feature in organ donors and is probably frequently accompanied by endotoxin absorption, leading to endotoxaemia and/or decreased endotoxin-inactivating capacity.

Use of hyperbaric oxygen in the treatment of extensive non-clostridial soft tissue infections

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The use of hyperbaric oxygen is a classical treatment for gas gangrene due to *Clostridium perfringens*. Its use in other anaerobic infections has been described but its efficacy in those cases has not been demonstrated.

During an African surgical experience we encountered severe soft tissue infections caused by other anaerobic organisms (*Peptostreptococcus*, *Bacteroides*, etc.). Because of the major social problems encountered by amputees in Africa, it is essential to try to avoid limb amputations.

We have treated 12 patients (one woman, 11 men) with advanced, extensive and life-threatening infections by using hyperbaric oxygen, appropriate antibiotic therapy and surgical excision. Ages ranged from 3 months to 67 years (average 32.5 years). There were three cases of Fournier's gangrene, five infections of open fractures and four other soft tissue lesions. A Comex two-position hyperbaric chamber was used. The number of sessions ranged from eight to 16 (average 11), their length was 1 h 15 min and the pressure used was 300 kPa.

There was one death (from Fournier's gangrene), but in 11 cases infection was controlled and amputation was avoided in all limb lesions.

In our experience hyperbaric oxygen therapy is an important adjunct in the treatment of extensive soft tissue infections due to anaerobic organisms other than *Clostridium perfringens*.

Bacteriuria during urinary tract catheterization: suprapubic versus urethral route: a prospective randomized trial

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Suprapubic urinary tract catheterization, either for urological reasons or for monitoring, is not a routine manoeuvre in general surgery, in spite of its theoretical advantage over the urethral route. This randomized trial compares infectious potential and tolerance of both methods.

Daily bacteriuria, measured with a technique detecting at least 10^3 colony forming units per millilitre, was used to determine the risk of infection. Each day patients were interviewed on the pain and discomfort induced by the catheter. In all cases, identical single-dose preoperative antibiotic prophylaxis was applied.

Patients ($n = 50$) were divided into two groups (25 suprapubic catheters and 25 urethral catheters). The mean ages of the two groups were similar, as were their sex and number of days of catheterization. Four patients had to be excluded because of an unsuccessful attempt to catheterize via the suprapubic route. All specimens cultured by suprapubic catheter remained sterile. Nine patients with a urethral catheter eventually developed bacteriuria. The difference became statistically significant on the third day of catheterization ($P < 0.05$) and was greater on day 4 and day 5 ($P < 0.01$). All nine bacteriuric patients maintained or increased their number of colony forming units per millilitre 48 h after removal of the catheter. Among these, seven were treated. Between the two groups, pain and discomfort did not achieve statistical significance.

Suprapubic catheterization is preferable to the alternative using the urethral route in terms of improving urine sterility.

Isolated hepatocytes and spleen fragments in intensive perfusion treatment of peritonitis

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The effect of intensive treatment of total peritonitis with isolated hepatocytes and xenospleen fragments has been studied.

A unique extracorporeal system consisting of a PF-05 blood fractionator, a MOST-1081 low-flow membrane oxygenator-thermo-exchanger and a device for keeping substrates such as hepatocytes and spleen fragments biologically active in the system was used in 36 patients with generalized purulent peritonitis for postoperative intensive treatment. Spleen fragments underwent cryopreservation and unfreezing in accordance with a special programme and so retained active metabolic effects. Fractionated, oxygenated and warmed blood plasma was perfused through spleen fragments and hepatocytes, mixed with a cellular blood fraction and returned to the patient.

The studies were performed 2, 24, 72 and 120 h after perfusion and demonstrated an improvement in tissue oxygen content compared with a control group of 20 patients managed by the traditional intensive treatment.

These findings suggest that further study of this unique method of treatment for peritonitis may be valuable.

Influence of local measures and surgical incision drapes in postoperative septic complications: a randomized prospective study

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Surgical wound infection is an important cause of morbidity and increased hospital stay. In order to reduce wound infection, antimicrobial solutions and incision drapes have been used.

A prospective randomized study has been performed in 160 patients undergoing abdominal surgery. The effect of skin preparation (aqueous or alcoholic povidone-iodine) and of incision drapes has been assessed. Swabs for bacteriological assessment were taken from the skin before surgery (specimen 1), after skin preparation (specimen 2) and just before skin closure (specimen 3).

The results of bacteriological culture and the type of surgery (clean, potentially contaminated, contaminated and infected) were correlated with the incidence of wound infection.

The groups were comparable with respect to age, sex, use of prophylactic antibiotics and type of surgery. Cultures grown from the three specimens were similar for all groups.

The incidence of infective complications was increased by the use of incision drapes (2.4 versus 11.3 per cent, $P < 0.01$). The incidence of infection increased with the degree of contamination of the surgical procedure, and was higher in the incision drape group in each case. The risk of infection was strongly influenced by positive culture from specimen 3. When drapes were used there was a correlation between the cultures obtained from specimens 1 and 3.

Incision drapes are ineffective in reducing septic wound complications.

Immunomodulatory role of macrophage activating cytokines in intra-abdominal sepsis

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The macrophage plays a pivotal role in immune response to infection. This study examined the effects of the macrophage activating cytokines (interferon γ (IFN- γ) and interleukin 4 (IL-4)) and their monoclonal antibodies (Mabs) in modulating host response to intra-abdominal sepsis.

CRW mice ($n = 198$) were given IFN- γ , IL-4, immunoglobulin G₁ (IgG₁), isotype control antibody (TRFK5), anti-IFN- γ and anti-IL-4. In study 1, mice ($n = 16$ /group) received *Escherichia coli* (33×10^6 organisms intraperitoneally) and 2 h later received cytokine, 10^4 units and Mab, 500 μ g bolus dose. In study 2, mice ($n = 15$ /group) underwent caecal ligation and puncture (CLP (dual puncture; 18G)) and were randomized to the same treatment groups and studied for survival. In study 3, mice ($n = 15$ /group) received CLP and cytokine, 10^4 units for 3 days or Mab, 100 μ g for 3 days in divided doses.

	IFN- γ	IL-4	IgG ₁	Anti-IFN- γ	Anti-IL-4
Study 1	25	—	0	65*†	—
Study 2	7	0	0	27‡§	0
Study 3	25	27	24	31	63#

Values are percentage survival. * $P < 0.001$ versus control; † $P < 0.05$ versus IFN- γ (χ^2 test); ‡ $P < 0.01$ versus control; § $P < 0.01$ versus IFN- γ ; # $P < 0.05$ versus control and IL-4 (log rank analysis)

IFN- γ and IL-4 were not protective 2 h after *E. coli* or CLP. Anti-IFN- γ offered significant protection against *E. coli* and CLP when given as a single dose. Bolus anti-IL-4 was not protective against CLP ($P = 0.08$ versus IgG₁), but divided administration conferred a significant survival advantage. Treatment with Mabs against IFN- γ and IL-4 was presumably by inhibiting excessive macrophage activation.

Treatment of peritonitis with multiple system failure

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This study analyses the mortality rate of patients treated with staged peritoneal lavage for diffuse peritonitis who had developed multiple failure of respiratory, circulatory, renal or hepatic systems.

From 1985 to 1991, 59 patients with diffuse peritonitis complicated by multiple system failure were treated with staged peritoneal lavage (26 women and 33 men, aged 14–81 years). Peritonitis was due to appendicitis (14), haemorrhagic pancreatitis (ten), intestinal suture dehiscence (nine), mechanical ileus (seven), mesenteric artery embolism (six), perforated peptic ulcer (six), biliary peritonitis (three), salpingitis (two), or traumatic rupture of the duodenum (one) or the large bowel (one). In all, 35 patients (59 per cent) were completely cured.

Failure of at least one system was observed in all 59 patients. Of the patients with only one system failure, all survived. Forty-two patients (71 per cent) had two-system failure, of whom six died. Three-system failure was observed in 26 patients (44 per cent), with eight deaths. In ten cases (17 per cent) more than three systems failed, and all these patients died (42 per cent of deaths).

The patients underwent repeat lavage every 24 h, from three to 15 times in all. Six patients who required the largest number of lavages died.

Complex intensive treatment together with staged peritoneal lavage is a method that gives the chance of saving over 50 per cent of patients with apparently fatal prognosis.

Percutaneous ultrasonographically guided drainage of abdominal abscesses

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Formation of abdominal abscesses is a continuing and life-threatening problem. The wider use of percutaneous drainage (PD) under ultrasonographic or computed tomographic control has led to an improvement in prognosis. In this paper the results of PD in 182 patients affected by intra-abdominal abscesses are evaluated.

From January 1984 to October 1991, 182 patients affected by intra-abdominal abscesses were treated by PD at our institutions. Patients' ages ranged from 8 to 82 (mean 56.3) years. Abscesses were spontaneous or post-traumatic in 107 cases (58.8 per cent) and postoperative in 75 cases (41.2 per cent). In 137 cases (75.3 per cent) abscesses were simple, in 45 (24.7 per cent) complex. Their size ranged between 2 and 19 (mean 7.5) cm. Drainage was performed in 26 cases (14.3 per cent) by simple or multiple needle aspiration followed by antibiotic injections. Direct insertion of a drainage catheter was performed in 20 cases (11.0 per cent). In 136 cases a catheter was inserted by a modified Seldinger technique. Simple abscesses were drained by one catheter; multiloculated or multiple abscesses required several catheters. In a case of multiple liver abscesses, percutaneous ultrasonographically guided catheterization of the portal vein for locoregional chemotherapy was performed. Catheters were left in place for a mean of 9.5 (range 4–15) days in simple abscesses and 30.8 (8–60) days in complex abscesses ($P < 0.005$). The success rate was 94.9 per cent (130 of 137 patients) in simple abscesses and 66.7 per cent (30 of 45) in complex abscesses. Overall success rate was 87.9 per cent. PD failed in 22 patients (12.1 per cent) in whom surgical drainage was performed. Multiloculation and the presence of necrotic tissue were the most common causes of failure. There were 17 critically ill patients for whom PD was the only possible therapeutic option. The mortality rate was 0.7 per cent (one case) in simple abscesses and 13.3 per cent (six cases) in complex abscesses. Overall mortality rate was 3.8 per cent. Nine PD-related complications were observed in seven patients (3.8 per cent): three enterocutaneous fistulae, two parietal haematomas, two mild cases of haemoperitoneum and two infections of the abdominal wall at the site of catheter penetration.

In conclusion, ultrasonographically guided PD of abdominal abscesses is indicated whenever feasible as a safe, gentle and relatively atraumatic procedure with few complications and late sequelae. In critically ill patients, PD of complex abscesses, despite the low success rate, often permits a clinical improvement with

subsequent reduction of postsurgical mortality rate. We underline the usefulness of portal ultrasonographically guided catheterization in the treatment of multiple liver abscesses.

Postoperative peritonitis and abscesses

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Although the majority of postoperative infections are limited to the surgical wound, the less frequent intra-abdominal infections, both diffuse and localized peritonitis, constitute a major clinical, diagnostic and therapeutic problem. The objective of the present study was to analyse 186 patients with postoperative peritonitis.

The sex ratio (male:female) was 1.9:1.0 with mean age of 59 (range 21–87) years. Sixty per cent of the patients suffered from malignant diseases. The original surgical operation involved the small bowel in 52 patients, the stomach in 68, colon-rectum in 46, biliary tract in 31, spleen in 12, and others in two. Previous surgery was considered as clean in 14 cases, contaminated in 60, clean-contaminated in 96 and dirty in 16. Some type of drainage was used in all but 11 (5.9 per cent) of the first operations. Fifty-three patients (28 per cent) presented with diffuse peritonitis while the rest presented with one (116), two (12) or three or more (five) abscesses. With respect to pathogenesis, 73 per cent (136) represented failure of an anastomosis, 15 per cent were from perioperative contamination and in 11 per cent continuation of a pre-existing peritonitis. Ultrasonography (US) was the most useful diagnostic procedure (76.3 per cent). Percutaneous drainage under US guidance was carried out as the first therapeutic step in 46 cases and surgery in 140. The predominant organism was *Escherichia coli* in both diffuse (72 per cent) and localized (87 per cent) peritonitis. Anaerobes were isolated in 38 per cent of cases with localized peritonitis and 17 per cent of those with diffuse peritonitis.

Percutaneous drainage was effective in 30 cases (65 per cent), partially effective in six and ineffective in ten. Reoperation for peritonitis was necessary in 22 per cent of those with diffuse peritonitis and 12 per cent of patients with localized peritonitis, due to persistent sepsis in 57 per cent of the cases. Overall mortality rate was 31 per cent (57 per cent after diffuse and 21 per cent after localized peritonitis). Higher mortality ($P < 0.01$) was observed in patients over 60 years of age and in patients with anastomotic failure and when the treatment was instituted after the first week of the previous surgery.

Perioperative contamination constitutes an important cause of postoperative peritonitis in this study. Effective prevention and early diagnosis and treatment could improve the poor outcome following postoperative peritonitis.

Significance of acetoacetate: hydroxybutyrate ratio in blood as an indicator of the severity of sepsis

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The purpose of this study was to measure the ratio of β -hydroxybutyric acid to acetoacetic acid as an early indicator of sepsis or multiple organ failure (MOF).

In patients with sepsis, oxygen consumption is reduced: energy production is therefore obtained by oxidation of free fatty acids, resulting in increased levels of reduced nicotinamide adenine dinucleotide. These levels inhibit the Krebs cycle, causing an increase in β -hydroxybutyric acid levels. The oxidative phosphorylation pathway is also inhibited, producing a further rise in β -hydroxybutyric acid levels.

Twenty patients with sepsis (12 men and eight women) with a mean age of 57.8 years were studied. Blood samples were taken twice daily at the same times (09.00 and 21.00 hours) and β -hydroxybutyric and acetoacetic acid levels were measured until the patients died or recovered from sepsis.

Patients who survived had a lower mean ratio than those who died and patients with MOF had a higher ratio than those with sepsis.

We conclude that the β -hydroxybutyric acid: acetoacetic acid ratio could be a good indicator of early sepsis and MOF, and of patient prognosis.

Surgical treatment of subphrenic abscesses

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Five cases of subphrenic abscess treated surgically during the period 1986–1991 are reported. The five patients were all men, mean age 69 (range 62–79) years. In four cases the subphrenic abscess occurred after gastrointestinal tract surgery and in one patient the abscess was chronic, developing after a sealed perforation of a gastrointestinal ulcer. The time between abscess formation and treatment varied from a few days to several months. The most common symptoms were persistent fever ($>38^{\circ}\text{C}$), abdominal pain and leucocytosis combined with pulmonary symptoms in two cases. Ultrasonography, computed tomography and radiographic studies with Gastrografin (Schering) proved helpful in diagnosis. Abscess was found to be left-sided in three cases and right-sided in two others. All patients underwent open drainage of the abscess followed by antibiotic treatment. Three patients had a satisfactory postoperative course, but one died from pulmonary embolism on the 25th day after surgery and the final patient is still in hospital.

Subphrenic abscesses frequently constitute a complication of gastrointestinal surgery and, despite advances in operative techniques, they still cause high morbidity and mortality worldwide. Prompt diagnosis is of great value and open surgical drainage followed by appropriate chemoprophylaxis is the recommended treatment.

Antibiotic prophylaxis in aortic surgery: intravenous versus intra-aortic administration

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Although aortic prosthetic infection is an uncommon event, the consequences are severe. Mortality and limb loss rates are high after aortic prosthetic infection and every effort, especially the use of prophylactic antibiotics, should be made to reduce the incidence.

This experimental study attempts to define which route of administration is optimal for antibiotic prophylaxis (intravenous versus intra-aortic) through pharmacokinetic studies of the levels of antibiotic in plasma and tissues, including the aorta. Theoretically, the value of the intra-aortic route is that the antibiotic can be administered directly to the area with greatest risk of infection (aortic anastomosis).

Twenty New Zealand White rabbits underwent a sham operation on the abdominal aorta. All rabbits received 60 mg kg^{-1} cefmetazole. In group A ($n = 10$) the antibiotic was administered intravenously and in group B ($n = 10$) the antibiotic was given intra-aortically during the operation. At the end of the operation the following samples were obtained: 4–5 ml venous blood, and tissue fragments of the abdominal wall (skin/subcutaneous tissue and muscle) and of the aortic wall. All samples were immediately frozen to -20°C and kept until further analysis. Cefmetazole levels in blood and tissue were studied with high performance liquid chromatography and the results are shown in the Table.

Group	Blood	Levels of antibiotic ($\mu\text{g ml}^{-1}$)		
		Skin/subcutaneous	Muscle	Aorta
A	221.56(28.56)	4.98(2.36)	2.24(1.47)	0.10(0.02)
B	517.75(106.12)*	4.30(4.23)	6.19(4.19)	1.00(0.54)

Values are mean(s.d.). * $P < 0.01$ versus group A (Student's t test). All other differences are not significant

In conclusion, these results suggest that intra-aortic antibiotics may be a useful alternative to intravenous prophylactic antibiotics when an aortic prosthetic graft is inserted.

A randomized comparison between an amoxycillin and clavulanic acid combination and cefotetan in elective colorectal surgery

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The value of antibiotic prophylaxis in elective colorectal surgery is well established and cephalosporins are widely used. The aim of this study was to assess, in a prospective, randomized, multicentre, clinical trial, the efficacy of amoxycillin and clavulanic acid (AC) versus cefotetan (C) in the prevention of postoperative infections.

Patients were given either AC (2.2 g) or C (2 g) in a single infusion on induction of anaesthesia. Failure of prophylaxis was defined as the development of infective complications, i.e. wound sepsis (minor infections), or abscess, peritonitis, septicaemia (major infections), within 30 days of operation.

A total of 208 patients was evaluated (105 AC, 103 C). The two groups were comparable for age, sex, surgical diagnosis and technical procedure. Eleven (10 per cent, 5 per cent confidence interval, 6 per cent) and 13 (13 per cent, 5 per cent confidence interval, 7 per cent) failures were observed respectively in the AC and C groups ($P = 0.23$, χ^2 test). There were nine major infections in each group. The infections occurred soon after surgery, the probability of success (determined by the method of Kaplan and Meier) decreasing slowly in both groups after the tenth day after operation.

Thus, it is concluded that in colorectal surgery AC and C show the same efficacy, in both the prevention of infection and the delay in occurrence of these infections.

Interleukin 2 and healing of intestinal anastomoses after blood transfusions

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In a previous study it was demonstrated in the rat that blood transfusions severely impair anastomotic healing and significantly increase susceptibility to intra-abdominal septic complications. Since it has been reported that blood transfusions suppress interleukin 2 (IL-2) production and that IL-2 stimulates wound healing, an investigation as to whether exogenous IL-2 can negate the effects of blood transfusions on anastomotic healing was undertaken.

In 80 Lewis rats an anastomosis was constructed in both the ileum and the colon. Rats subsequently received either 3 ml saline (control and IL-2 groups) or 3 ml blood from Brown Norway donors (BT and BT/IL-2 groups), intravenously. From operation onwards animals in the IL-2 and BT/IL-2 groups received 4.5×10^5 units recombinant human IL-2 day^{-1} subcutaneously, while rats in the other groups received 5 per cent dextrose. The animals were killed 3 or 7 days after the operation and examined for intra-abdominal septic complications and anastomotic strength. Bursting pressures were as follows:

	Ileum bursting pressure (mmHg)		Colon bursting pressure (mmHg)	
	3 days	7 days	3 days	7 days
Control	86(15)	293(35)	118(20)	236(20)
IL-2	29(7)*	242(20)*	56(8)*	184(15)*
BT	32(8)*	227(16)*	58(10)*	164(11)*
BT/IL-2	63(9)†	299(18)†	87(7)†	237(8)†

Values are mean(s.d.). * $P < 0.005$ versus control; † $P < 0.0005$ versus BT (Kruskal–Wallis test)

In addition, an abscess was found around 60 per cent of the ileal anastomoses and 40 per cent of the colonic anastomoses in the BT group, while no abscess was seen in the control group and the groups receiving IL-2. In the last, fibrin deposits were seen around the anastomoses.

This study shows that, under normal conditions, IL-2 impairs the healing of intestinal anastomoses but that it reverses, at least partly, the negative effects of blood transfusions.

Laparoscopic procedures

Laparoscopic highly selective vagotomy

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We consider laparoscopic highly selective vagotomy to be the surgical treatment of choice for chronic duodenal ulcer. A consecutive series of nine patients (eight men and one woman) with documented chronic duodenal ulcer was treated between February and September 1991. The mean age was 36 (range 27–56) years. Indication for surgery was failure of medical treatment. The mean duration of the disease was about 9 (range 3–13) years. Patients were operated on under general anaesthesia with endotracheal intubation. A Faucher tube was inserted into the stomach to stretch the greater curvature. Pneumoperitoneum was obtained by umbilical puncture. Four cannulae were needed. First, the endoscope was inserted through a 10-mm cannula at the upper limit of the umbilicus. The procedure began with abdominal visual exploration and the nerve of Latarget was easily identified. A 5-mm cannula was introduced to the right of the xiphoid process and allowed the placement of an irrigator-aspirator cannula which helped to retract the left hepatic lobe. Two other 10-mm cannulae were placed beneath each costal margin to introduce the grasping forceps, scissors, hook coagulator and clip applicator. The dissection proceeded upward from the crow's foot. The anterior leaf was divided close to the lesser curvature. The main vessels were doubly clipped and divided while the smaller generally higher ones were coagulated. The separation of the posterior leaf was facilitated by opening the lesser sac. The lower 6 cm of oesophagus was completely bared. To make this critical step easier a rubber sling was placed around the oesophagus. There was no mortality nor operative morbidity. Patients were discharged after 4 (range 3–5) days. The mean operative time was 180 min. The acid secretion test under insulin stimulation confirmed the completeness of the vagotomy. Laparoscopic highly selective vagotomy promises to be as efficient and safe as its open counterpart. Moreover, it benefits from the advantages of the laparoscopic approach within a reasonable operative time.

Preliminary results of laparoscopic Nissen fundoplication

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The main postoperative problems of antireflux surgery (pain and ileus) are due to the laparotomy. In order to minimize the postoperative discomfort, we attempted antireflux surgery by laparoscopy. The aim of this study was to evaluate the preliminary results of this method.

Fourteen patients (six men, eight women) of median age 44 (range 22–67 years) underwent surgery. All had clinical signs of gastro-oesophageal reflux; 12 had endoscopic signs of oesophagitis. The percentage of time during which pH was less than 4 ranged from 14 to 90 per cent. The operation was commenced by laparoscopy in all cases, but conversion to open surgery was necessary in two cases. Four to seven ports were necessary. A floppy Nissen fundoplication was achieved by laparoscopy in 12 cases. The gastro-gastric suture was performed by a continuous suture in the first three cases and by stapling in the following nine procedures. The operation was completed by truncal vagotomy in two cases and by cholecystectomy in six cases.

The duration of operation ranged from 90 to 210 min, the mean postoperative hospital stay (patients with laparotomy included) was 4.5 (range 3–7) days; in laparoscopic procedures it was only 3.5 (range 3–5) days. Oral food intake was started on the first postoperative day. Two complications (one wound haematoma and one pleural haemorrhage) occurred. After operation (follow-up 1–8 months) clinical signs of reflux were relieved in all cases. Endoscopy performed in four cases showed no oesophagitis; the pH test performed in five patients showed that acid reflux (pH <4) lasted less than 8 per cent of the time.

In conclusion, these results demonstrate that laparoscopic Nissen fundoplication is feasible. The preliminary results are encouraging but further evaluation is necessary.

Taylor's vagotomy by laparoscopy in the treatment of chronic duodenal ulcer

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Surgery by videolaparoscopy has been used in 50 patients, mean age 33 (range 19–55) years, to treat chronic duodenal ulcers resistant to medical treatment for 2 years (antacid, anti-H₂, Omeprazole) with a mean 2.8 recurrences under medical treatment.

After the lesser omentum is opened, the hiatus is recognized by retracting the left lobe of the liver and the right crus of the diaphragm. Traction on the right crus allows the right vagal trunk to be freed with the hook. This is cut between two clips and a piece sent for histological examination. The anterior seromyotomy is performed from the cardiac junction to the 'crow's foot' at a distance of 1.5 cm from the lesser curve, with haemostasis of the small vessels of the anterior gastric wall. With the magnification, it is possible to preserve the mucosa which can be recognized by its blue colour. The seromyotomy is closed by an overlap suture tied intracorporeally with application of fibrin sealant.

The follow-up in the 50 patients was uneventful without mortality and morbidity. The hospital stay was limited to 5 days. The results are similar to those for open surgery with healing of the ulcer in all cases and a reduction in mean (s.e.m.) acidity tested by BAO and MAO of 79(1.3) per cent and 83(1.2) per cent. The follow-up was 2–24 months. One patient had to undergo reoperation for oesophageal reflux.

A prospective study has been initiated to evaluate the results of this minimally invasive surgery.

Highly selective vagotomy: laparoscopic approach

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This retrospective study analysed the feasibility of highly selective vagotomy (HSV) under laparoscopy.

Laparoscopic HSV was performed on 21 patients between February and October 1991. There were 17 men and four women with a mean age of 38 (range 17–58) years. Indication for surgery was chronic duodenal ulcer in 17 patients with a mean duration of the disease of about 8 (range 3–24) years. In four other cases, the HSV was associated with a Nissen fundoplication for peptic oesophagitis.

The three most important steps were recognition and sparing of the crow's foot, division of the two leaves of the lesser omentum and complete dissection of the lower 6 cm of oesophagus. The main vessels were clipped and divided while the smaller were coagulated. Two cholecystectomies and six fundopexies were also performed. The mean operating time was 200 (range 135–420) min.

There was no mortality and little morbidity: two patients complained of shoulder pain and eight of transient dysphagia. All patients were discharged after 4 (range 3–6) days. Barium swallow was performed in 18 patients, and showed two gastropareses and one oesophagogastric reflux. Nine gastroscopies were done, and all showed complete healing. In the four patients investigated by acid secretion tests, the mean decrease in the maximal output after pentagastrin stimulation was 62 per cent.

In conclusion, HSV can be done safely with a low morbidity rate under laparoscopy. A prospective study with gastric secretory tests is in progress to confirm the quality of vagotomy by the laparoscopic approach.

Complete laparoscopic therapy of gallbladder and common bile duct stones

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There are many variations in biliary anatomy, and the preoperative diagnosis of common bile duct stones is either ineffective or expensive.

Preoperative ultrasonography diagnosed common bile duct stones in only 3 per cent of patients in this study. Of patients undergoing laparoscopic cholecystectomy a successful cholangiogram was obtained in 98 per cent of cases, and in these the incidence of duct stones was 11 per cent.

There are new methods of clearing the common bile duct laparoscopically. Laser-lithotripsy with water-flushing has frequently been effective, while in some cases extraction using a Dormia basket, dilatation of the ampulla of Vater and microdrainage of the common bile duct is required. After apparently complete laparoscopic choledochoscopic clearance of the duct, only three of ten patients required endoscopic sphincterotomy.

Laparoscopic treatment of common bile duct stones

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During the initial experience of 68 different general surgeons who recruited 3244 patients in this prospective multicentre study, 58 patients (1.8 per cent) with common bile duct (CBD) stones detected by intraoperative cholangiography were submitted to attempted laparoscopic treatment of CBD stones. The mean number of stones detected during intraoperative cholangiography was 2.2. A group of 23 patients presented with a history of stone migration. During laparoscopy, 16 patients (28 per cent) were immediately converted to laparotomy for standard choledochotomy and T tube drainage. Four patients were treated by transcystic drainage, leading to one secondary conversion to laparotomy, two postoperative endoscopic sphincterotomies (ESs) and one successful treatment with normal postoperative cholangiography in a patient submitted before operation to ES. A total of 38 patients (66 per cent) was submitted to an attempted laparoscopic treatment of CBD stones, including instrumental Dormia extraction in 27 patients, transcystic endoscopic extraction in seven patients, CBD lavage in three patients and laparoscopic choledochotomy with T tube insertion in one patient. The laparoscopic procedure of CBD stone clearance was complete in 26 patients and incomplete in 12, leading to four conversions to laparotomy during the procedure, and postoperative ES in the remaining eight patients. The overall success rate of laparoscopic treatment of CBD stones was 47 per cent with a conversion rate to laparotomy of 36 per cent and to postoperative ES in 17 per cent. Postoperative complications were one death at 1 month (2 per cent), one patient with transient biliary leak and another with subphrenic abscess. In conclusion, in patients with CBD stones during laparoscopic cholecystectomy, the overall conversion rate is 36 per cent and ES is required in 17 per cent. When laparoscopic CBD stone clearance is tried, the success rate is 61 per cent (23 of 38 patients) with a low incidence of postoperative complications.

Experience in colonic laparoscopic surgery

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From May 1990 to November 1991, 21 patients (aged 36–90 years) underwent the following procedures: drainage of peritonitis from colonic diverticular perforation in one patient, colostomy transposition in one, reversal of Hartmann's procedure in two, and 17 patients had a colectomy. Of the 17 patients who had a colectomy, six had diverticular disease, seven had large polyps (four Duke's A), three had palliative resection for invasive adenocarcinoma and one for volvulus. Colectomy was right-sided in three, left-sided in 13 and transverse in one.

For colectomy a 30-mm incision was made, thus allowing the removal of resected colon in all cases, and extra-abdominal anastomosis in 11 cases.

The mean duration time of operation was 3 (range 1.3–5) h. One unsuccessful dissection at the beginning of the series required a laparotomy.

In 18 cases there were no subsequent problems and patients remained in hospital for a mean of 6 days. Complications were failure resulting in one conversion, one prolonged ileus (patient left hospital 10 days later) and one postoperative bleeding followed by an anastomotic leakage which necessitated a second operation 2 days later (drainage and colostomy).

Videolaparoscopic colonic surgery offers the same advantage as any minimally invasive surgery: less pain, earlier intestinal transit

resumption and shorter hospital stay. The morbidity rate does not seem to exceed that for conventional surgery.

These results suggest that the best indications for laparoscopic surgery are reversal of Hartmann's procedures, and the treatment of polyps that cannot be treated endoscopically because of their size or location. Failures or complications of endoscopic polyp treatment (e.g. perforation or bleeding) can also be treated laparoscopically. In the future it should be possible to use this technique for the treatment of invasive cancers without compromising oncological principles.

Symptomatic outcome 1 year after laparoscopic cholecystectomy

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It has been speculated that the symptomatic outcome after laparoscopic cholecystectomy (LC) may be better than with open cholecystectomy. To assess this we sent a standard questionnaire to 92 patients who had undergone laparoscopic cholecystectomy 12 months or more before. The same questionnaire was sent to patients who had had open cholecystectomy (OC) ($n = 167$) and inguinal hernia repair (IH) ($n = 163$) in our unit at least 12 months before. Patients were asked to classify frequency of selected symptoms experienced in the preceding 6 months as 'every day', 'most days', 'occasionally' or 'never'. We have previously used this technique to assess outcome after duodenal ulcer surgery¹. The percentage having symptoms 'every day' or 'most days' and patients' assessment are shown below.

	LC ($n = 92$)	OC ($n = 167$)	IH ($n = 163$)
Stomach pain	4.3	6.6	6.1
Nausea/vomiting	9.8	3.6	5.0
Heartburn	12.0	9.6	10.4
Bloating	10.8	14.3	5.0
Belching	15.2	20.3	14.1
Antacid consumed	21.8*	12.0	15.3
Operation a success	93.4	95.2	94.4
Symptoms cured or improved	94.6	94.0	94.4

* $P < 0.05$

There was no significant difference in the number of patients who considered their operation a success and their symptoms cured or improved. The patients who had undergone laparoscopic surgery consumed significantly more antacids and had a higher incidence of nausea or vomiting than those who had had open cholecystectomy. We conclude that there is no long-term symptomatic advantage gained by patients undergoing laparoscopic compared with conventional cholecystectomy.

1. Macintyre IMC, Millar A, Smith AN, Small WP. Highly selective vagotomy 5–15 years on. *Br J Surg* 1990; 77: 65–9.

Limitations of capnography during anaesthesia for laparoscopic surgery with intraperitoneal carbon dioxide

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In this prospective study of cholecystectomy by laparoscopy with carbon dioxide insufflation the following data were measured: arterial pressure of carbon dioxide (P_{aCO_2}), end tidal pressure of carbon dioxide (P_{etCO_2}), pressure gradient ($P_{aCO_2} - P_{etCO_2}$) and pH at different times: 5 min before T_5 and at the start (T_0) of laparoscopy, 15 min (T_{15}) and 60 min (T_{60}) after the start of laparoscopy and then every 60 min.

A total of 33 patients, American Society of Anesthesiologists (ASA) grades I and II, mean age 52.5 years, without pre-existing respiratory pathology, was included in the study from December 1990 to September 1991. The general anaesthesia procedure was the same for each patient; controlled ventilation was adapted to the variation

Laparoscopic procedures

of P_{etCO_2} by modification of the respiratory rate and tidal volume. Mean (range) duration of anaesthesia was 188 (60–210) min. There was no operative death and no anaesthetic accident.

The results showed an increased P_{aCO_2} and a decreased pH with time despite a P_{etCO_2} maintained constant by adaptation of the respiratory parameters. The gradient increased with time. This indicates that respiratory monitoring using P_{etCO_2} measurement has its limitations and underestimates the real P_{aCO_2} ; the respiratory acidosis which appears and increases with the duration of the surgery is not controlled by modification of the ventilation.

	P_{aCO_2} (mmHg)	P_{etCO_2} (mmHg)	pH	Gradient
T_{-5} ($n = 33$)	38(4.7)	32(4.3)	7.42(0.04)	5.4(1)
T_{15} ($n = 33$)	42(6.4)	36(5.7)	7.38(0.05)	7.4(8)
T_{60} ($n = 33$)	44(8.4)	35(6.4)	7.36(0.05)	10.7(9)
T_{120} ($n = 21$)	46(7.9)	35(7.2)	7.34(0.05)	14.1(1.7)
T_{180} ($n = 7$)	48(5.2)	36(4.1)	7.30(0.04)	11(2.1)

Values are mean(s.d.)

The results suggest that a safety limit of duration of anaesthesia could exist for laparoscopic surgery with carbon dioxide insufflation.

A difficulty score in laparoscopic cholecystectomy

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The aim of this study was to evaluate the possible advantages of establishing a difficulty score in laparoscopic cholecystectomy.

We have divided the procedure into four phases: (1) peritoneal cavity access; (2) gallbladder appearance; (3) triangle of Calot dissection; and (4) cholecystectomy. Each phase was scored from 0 to 3 according to difficulty, and each degree was clearly defined. The final score results from the sum of these four values. We have prospectively tested this score in our first 250 cases; a univariate analysis was performed, matching score to operation time, conversion rate and complication rate.

A significant correlation ($P < 0.0001$) was found between score and operation time, confirming that this score allows an objective measurement of operative difficulties in laparoscopic cholecystectomy.

This measurement may be of use in making correlations with preoperative situations (clinical, biological, imaging) to allow selection of patients. Moreover, it can be used for checking trainees' operating curricula and for establishing a computerized operation report.

Laparoscopic cholecystectomy: postoperative complications in 130 cases

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Of 130 cholecystectomies performed in 1 year, the postoperative course was uncomplicated in 108 patients (83.1 per cent); the mean (range) hospital stay in this group was 2.8 (1–4) days. Seventeen patients (13.1 per cent) had very intense abdominal and/or scapular pain after incomplete evacuation of the pneumoperitoneum at the beginning of our practice. Two benign abdominal complications occurred at the umbilicus: an early evisceration of a small piece of omentum through a non-closed fascial defect and an infection after acute cholecystitis. There were three abdominal complications (2.3 per cent): a subhepatic and perihepatic haematoma evacuated by computed tomography-guided drainage, a biliary leak caused by slippage of a cystic duct clip, and an iatrogenic injury to the common bile duct treated by a Roux-en-Y loop. The reintervention rate was 2.5 per cent. The mean hospital stay in this group was 18.2 days.

Six patients were rehospitalized in the week after discharge: five for abdominal or deep-seated abdominal pain, and one with a raised serum amylase level most probably caused by migration of a cystic duct stone.

This analysis of the postoperative course constitutes the best way of evaluating a new technique. It confirmed the pre-eminence of the biliary risk that occurred at the beginning of our experience in young patients with uncomplicated cholelithiasis. Training and experience as well as great care by the surgeon should improve the quality of a benign operation that should cause no harm to the patient.

Postcholecystectomy symptoms following laparoscopic cholecystectomy

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Abdominal symptoms persist in 30 per cent of patients after open cholecystectomy and biliary lithotripsy. Laparoscopic cholecystectomy is now the treatment of choice for symptomatic gallstone disease. No data exist as to the influence of laparoscopic cholecystectomy on symptoms. We analysed 100 patients who had undergone laparoscopic cholecystectomy a median of 13 (range 11–19) months previously. Preoperative and postoperative symptoms were compared and patient satisfaction (PS) (median and range) was graded from one (worst) to five (best). Mean(s.d.) time to resumption of full activity (TFA) was recorded. All patients had more than two symptoms before operation.

	Postoperative symptoms				Total
	None	1	2	> 2	
Number	52	19	14	15	100
TFA (weeks)	2.3(1.5)	2.7(1.4)	2.3(1.3)	2.6(2.8)	2.4(1.7)
PS	5(5–5)	5(4–5)	5(3–5)	4(2–5)	5(2–5)

These data indicate that most patients return to full activity within 3 weeks of laparoscopic cholecystectomy. However, 29 per cent of patients have persistent symptoms (at least two postoperative symptoms) and satisfaction with the operation appears to correlate with these symptoms. Thus, the incidence of postcholecystectomy symptoms is similar after laparoscopic and open cholecystectomy and biliary lithotripsy. Patients should be advised of the risk of persistent symptoms after these procedures.

Old age: a good indication for laparoscopic cholecystectomy

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This study evaluated the safety and usefulness of laparoscopic cholecystectomy (LC) in elderly patients, with regard to preoperative anaesthesia, surgical problems and postoperative course.

The first 250 patients were evaluated prospectively, and two groups were compared: group 1, 18 elderly patients (over 70 years) and group 2, 44 control patients (age 40–50 years). The following parameters were compared by means of Student's t test: clinical pattern (complicated or not), difficulty score, operating time, anaesthetic problems, conversion rate, complication rate, postoperative ileus and hospital stay.

Statistical difference was noted for clinical complications (worse in elderly patients, $P < 0.05$), difficulty score ($P < 0.0001$), operating time ($P < 0.0001$) and hospital stay ($P < 0.0001$). No difference was noted for anaesthetic problems, conversion rate, complication rate and postoperative ileus.

These results confirm the more advanced pathology and surgical complications of cholelithiasis in elderly patients; nevertheless the postoperative course is not more complicated in these patients when treated by LC; no anaesthetic complication was responsible for conversion to laparotomy, and no more pulmonary or local complications occurred; the longer hospital stay (6.8 versus 4.2 days) was not related to intestinal or general problems but rather to prudence in delaying discharge in elderly patients treated by a new method.

We conclude that LC can be undertaken in elderly patients with good results and with a low complication rate.

Late biliary peritonitis after laparoscopic cholecystectomy

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A 70-year-old woman was admitted to our department 1 week after laparoscopic cholecystectomy performed in a district hospital. Two days previously she had begun to complain of abdominal pain and discomfort. Neither fever nor abdominal guarding was present. Abdominal ultrasonography (US) showed fluid in the pelvis and in Morrison's pouch. Fluid was aspirated through a Chiba needle; morphological culture was negative. The patient was discharged with antibiotic therapy and was clinically well. She was readmitted 1 week later with recurrence of symptoms and reappearance of fluid on US. Pigtail drainage was established in the pelvis with complete resolution of symptoms. Because of continuing drainage of bile in the next 3 days, cholangiography and computed tomography were performed; bile leakage was demonstrated near the clips on the cystic duct. Exploratory laparotomy was performed through a right subcostal incision. After cleaning the abdominal cavity of bile and fibrin, the common duct was exposed. The two clips were found open on two sides of the remnant of the infundibulum, allowing bile leakage. An intraoperative transcystic cholangiogram allowed exclusion of further leakage. After ligation of the cystic duct with removal of the remnant of the infundibulum, suction drainage was performed in Morrison's pouch and the abdomen was closed. Postoperative recovery was uneventful and the patient remains well 3 months later. This case emphasizes the importance of placing the clips on the cystic duct after it has been fully cleared to avoid inclusion of the infundibulum instead of the cystic duct.

Safety of laparoscopic cholecystectomy in high-risk patients

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The safety and results of laparoscopic cholecystectomy in high-risk patients have not been prospectively investigated. During an 18-month period, 30 of 230 consecutive patients undergoing this operation were classified as ASA grade III (American Society of Anesthesiologists criteria). Compared with the ASA I and II group of patients ($n=200$), ASA III patients were significantly older (65 versus 50 years) and presented with a higher incidence of risk factors (mainly cardiovascular) and acute cholecystitis ($P<0.05$). Preoperative risk factors were cardiac (70 per cent), vascular (23 per cent), chronic obstructive airway disease (13 per cent), immunosuppressive drugs (10 per cent) and presence of diabetes or cirrhosis (7 per cent).

In the ASA III group of patients, the mean duration of pneumoperitoneum, the conversion rate to laparotomy (10 per cent), the mean postoperative hospital stay (3.6 days) and the occurrence of general and local complications after operation (10 per cent) were not significantly different from those in the other groups. In ASA III patients, postoperative complications included minor general (hyperthermia, one case; ileus and pneumonia, one case) and local (parietal infection, one case) complications.

In conclusion, even in high-risk patients (older and with more preoperative risk factors), and in the more difficult cases in this group (increased incidence of acute cholecystitis), results of laparoscopic cholecystectomy remain excellent, with low morbidity rates, short postoperative hospital stay and excellent postoperative comfort for the patient.

Cost of laparoscopic cholecystectomy: results of the first 42 cases in a French teaching hospital

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A prospective study was conducted to compare the direct and indirect costs of surgical treatment of gallstones by laparoscopy with those of conventional open surgery. Preliminary results relate to direct hospital costs for the first 42 patients (33 women, nine men) treated laparoscopically, compared with existing French data on the cost of conventional cholecystectomy.

All patients had symptomatic gallbladder disease with no biliary duct obstruction. Mean (s.d.) age was 46.2(14.7) (range 25–79) years. No complications were noted.

Costs calculated (all given as mean (s.d.)) included all direct medical costs incurred during the hospital stay, i.e. medical and other staff salaries, medications, laboratory tests, radiography and other investigations, operating room costs, including anaesthesia and depreciation of specific laparoscopic equipment.

Average length of stay was 4.33(1.34) (range 3–8) days. Duration of surgery was 116.0(44.6) (range 50–230) min, compared with 78 min for open surgery¹. Total cost was 10949.49 (2291.9) (range 764.13–16022.98) French francs (Fr). The cost of preoperative examinations was 1534.26(429.56) Fr, the cost of the operating theatre was 4949.79(1262.78) Fr, the postoperative cost (examinations and drugs) was 138.61(207.29) Fr, and the cost of daily medical and nursing care was 4326.83(1319.39) Fr. According to D'Alche-Gautier *et al.*¹, the operating theatre cost for open surgery with comparable definitions was 1210.4 Fr. However, average length of stay in their study was 8.3(3.1) days, compared with 4.33 days for laparoscopy, implying an average total cost for one stay of 10555.92 Fr.

In conclusion, direct hospital costs for laparoscopic cholecystectomy and conventional surgery seem to be very similar, the higher operating room cost of the former being compensated for by a much shorter length of stay. This result will be validated by the final results of our study, which will also include direct and indirect costs after discharge from hospital.

1. D'Alche-Gautier MJ, Lecoutour X, Soufarapis H. Le coût direct de la cholecystectomie au CHU de Caen en 1989. *J d'Economie Méd* 1991; 9: 4–5, 223–38.

Laparoscopic cholecystectomy: experience of a Brussels suburban hospital

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Between May 1990 and November 1991, 117 laparoscopic cholecystectomies were performed at this centre. Mean age of patients was 53 (range 16–92) years. Eight (6.8 per cent) laparoscopies were converted to laparotomy for technical difficulties.

Preoperative investigations in all patients included gallbladder ultrasonography, oral cholecystography, intravenous cholangiography and occasionally common bile duct (CBD) computed tomographic scanning for diagnosis of CBD stones. If the preoperative work-up was suggestive of CBD stones, endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy was performed before operation (25.6 per cent of cases). Five adhesiolyses and two hepatic biopsies were performed together with laparoscopic cholecystectomies. Operative drainage was performed in five cases and systemic prophylactic antibiotics (cephalosporin) were given to all patients.

There was no hospital mortality and no extrabiliary morbidity. There was one case of biliary morbidity (0.85 per cent) (a bile duct injury occurred in one case of acute cholecystitis). Despite positive bacteriobilia in 25 of 117 cases (21.3 per cent), no postoperative abscesses occurred. The mean postoperative hospital stay was 3.6 days (90 per cent left hospital on the first or second postoperative day). To date no residual CBD stones have been found at follow-up.

Laparoscopic cholecystectomy appears to be a safe procedure with functional benefit for patients. Careful selection of patients, with conversion to laparotomy for difficult cases, is mandatory to avoid intra-abdominal complications.

Laparoscopic versus open cholecystectomy: a prospective controlled study

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This study was performed to audit the use of open and laparoscopic surgery in a university hospital.

Since May 1990 laparoscopic cholecystectomy has been performed in our hospital. Since then all elective cholecystectomies and all emergency operations that can potentially be performed laparoscopically are performed using the laparoscopic technique.

Laparoscopic procedures

Patients were studied prospectively and compared for indications, complications, hospital stay, analgesia and demographics.

From May 1990 to April 1991 100 laparoscopic cholecystectomies were performed. In the same period 84 open cholecystectomies were carried out. In 18 laparoscopic procedures the operation was converted to open cholecystectomy. There were no serious complications in either group with one reoperation in each group. The hospital stay averaged 6.3 *versus* 11.2 days in the conventional group.

Although there are no randomized controlled studies comparing open with laparoscopic surgery, there seems to be an advantage of the laparoscopic technique in certain patients. There is, however, a learning period in almost all institutions with a higher rate of complications. Our two groups are not directly comparable, since only those who were excluded from laparoscopic surgery were operated on conventionally. A trend of shorter hospital stay and better patient comfort was seen in the laparoscopic group. The complications, however, are comparable if not fewer in the conventional group compared with the literature, where serious bile duct injuries are reported in one in 100 operations.

We conclude that laparoscopic cholecystectomy is a safe technique when performed or assisted by experienced surgeons, but one should not hesitate to convert to open surgery when any unclear or difficult situations arise.

Indications for open cholecystectomy in the era of laparoscopic surgery

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Of 142 cholecystectomies performed for cholelithiasis in 1 year, 16 (11.3 per cent) were carried out by the classical open method. The indications for open operation were: non-complicated cholelithiasis ($n = 6$) either because of non-availability or breakdown of the equipment before a second camera was available or because of a lack of experience of a young surgeon; multiple adhesions secondary to a previous operation for perforated ulcer ($n = 1$); empyema of the gallbladder in old and fragile patients ($n = 5$); and conversions from an attempt at laparoscopic surgery for acute cholecystitis either because of bleeding ($n = 2$), the slippage of the cystic duct clip in the presence of severe inflammatory changes ($n = 1$) or an empyema with adenocarcinoma of the gallbladder ($n = 1$).

The mean age of this group was 55.4 (range 30–91) years, which is similar to the age of patients who had cholecystectomy before the introduction of laparoscopy (53.9 years) but higher than the group treated by laparoscopy (42.7 years).

There was no mortality, but there were six complications (two wound infection, three lymphangitis and one atelectasis). The mean hospital stay was 8.5 (range 5–23) days, which was longer than in the laparoscopy group with a mean stay of 2.8 (range 1–7) days.

At present, the indications for open cholecystectomy, apart from the failure or the impossibility of laparoscopy, remain essentially acute presentations in fragile patients and certain cases of associated choledocholithiasis.

Qualitative indicator for the appraisal of laparoscopic cholecystectomy

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When describing or comparing different series of laparoscopic cholecystectomy, the global percentage of conversions into laparotomy cannot be used alone as a good indicator of success. In fact, a conversion may have two opposite goals: either to avoid a complication (elective conversion) or to solve it (forced conversion). On the other hand, a reoperation can be considered as an omitted or delayed conversion, because a laparotomy is done to solve a problem that occurred but was not detected during laparoscopy.

We propose a 'ratio of the quality of conversion' (R_{QC}) that takes into account these three concepts as a useful qualitative indicator of surgical assessment in laparoscopic cholecystectomy.

$$R_{QC} = \frac{EC}{EC + FC + DC} \times 100$$

where EC is the number of elective conversions, FC is the number of forced conversions and DC is the number of delayed conversions.

If the amplitude of indications is adapted to the experience of the procedure, this ratio should always stay at a high level, regardless of the percentage of simple or complicated laparoscopic cholecystectomies performed.

Obesity is not a contraindication to laparoscopic cholecystectomy

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Any surgical operation in an obese patient may lead to parietal and/or lung infection. Laparoscopic surgery seems to minimize such complications. We analysed our first 250 cases of laparoscopic cholecystectomy to assess the effect of obesity on the occurrence of complications with this operation.

We calculated for each patient the percentage excess weight by the Lorentz formula and assigned the patients to five groups: group I (excess weight <0 per cent), 58 patients; Group II (0–10 per cent excess weight), 46 patients; group III (10–20 per cent excess weight), 43 patients; Group IV (20–30 per cent excess weight), 48 patients; group V (excess weight >30 per cent), 51 patients; not calculated in four patients. For each group we evaluated mean difficulty score, mean operating time, conversion rate, complication rate and mean hospital stay. Statistical analysis was performed by Student's *t* test.

No difference was noted between the five groups in mean operating time, conversion rate, complication rate and hospital stay. A statistical difference was noted in the judgement of operative difficulty. No parietal sepsis occurred in obese patients and no minor or major pulmonary problem was noted.

Our analysis indicates that laparoscopic cholecystectomy is a safe and useful technique for obese patients with symptomatic cholelithiasis.

Relevance of a new classification of complications of surgery: examples in open and laparoscopic cholecystectomy

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Adoption of a standard classification of complications may solve numerous surgical problems. We have recently proposed a standard classification of complications based on four grades of severity¹. This classification was used retrospectively in 1252 patients treated by elective open cholecystectomy in a North American and a European centre, and prospectively in the first 181 patients treated by laparoscopic cholecystectomy in the North American centre.

In the open cholecystectomy group, 12 per cent and 14 per cent of the patients developed complications in each centre, respectively. Approximately 6 per cent of the patients developed grade I (minor) complications. Grade II complications (without residual disability) were noted in 6 per cent and 8 per cent, and grade III (with residual disability) in 0 and 0.3 per cent, respectively. There were no grade IV complications (deaths). Using univariate and multivariate analysis, individual risk factors for developing the different categories of complications were different between centres, whereas two preoperative scoring systems, the American Society of Anesthesiologists' criteria and a simplified APACHE II, were found to be predictive for all types of complications in both centres.

In the laparoscopic cholecystectomy group there were only 6.1 per cent grade I complications without other types of complication. This small number of complications did not allow the identification of significant risk factors.

The present study demonstrates the advantages of a uniform way of reporting surgical complications, namely: (1) the ability to compare results of surgery between different centres in a standardized fashion; (2) the ability to compare results of different treatments; (3) the ability to identify local and general preoperative risk factors as well as preoperative prognostic scores. The general

implementation of such a classification system will allow meaningful meta-analysis to be performed.

1. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. *Surgery* 1992; **111** (in press).

Diminished inspiratory muscle strength after open cholecystectomy versus laparoscopic cholecystectomy

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Controversy exists as to the significance of the abdominal incision in respiratory complications after open cholecystectomy. We tested maximal inspiratory effort (P_{iMax} in millimetres of mercury) in groups of patients undergoing open cholecystectomy (OC) and laparoscopic cholecystectomy (LC). Measurements were taken at 24-h intervals for the duration of the hospital stay. A third group of patients undergoing lower limb surgery were used as controls. Each group was matched for age, sex and anaesthetic time.

Group	n	Time (h)					
		0	24	48	72	96	120
Controls	12	123.1	100.9*	127.3	125.7	—	—
LC	25	118.8	98.2*	113.8	117.0	—	—
OC	12	112.5	82.5*	81.3*	84.3*	94.1*	111.7

* $P < 0.5$ versus zero hour value

The results indicate that there is a significant decrease in maximal inspiratory effort after operation for up to 24 h in all groups. This effect is prolonged in the open cholecystectomy group for up to 4 days. These data suggest that the abdominal incision in open cholecystectomy significantly affects the maximal inspiratory effort after operation.

Laparoscopic cholecystectomy: social and economic impact

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The arrival of laparoscopic digestive surgery, and especially of cholecystectomy, has greatly modified the recruitment of patients and the surgical indications for cholelithiasis. After 1 year of practice (1990–1991), the results were compared with those of open cholecystectomy performed during the previous year (1989–1990). The sex ratio was identical (75 versus 71 per cent women), but laparoscopic surgery led to: an increase in the numbers undergoing operation from 33 to 130 (400 per cent), and a wider range of indications to include more patients with symptomatic and non-complicated forms (74 versus 48 per cent), asymptomatic lithiasis (8 versus 0 per cent), younger age (40.2 versus 54.9 years, $P = 0.02$) and active employment (54 versus 29 per cent, $P = 0.05$). There was a shorter mean hospital stay (3.3 versus 5.1 days), a shorter recovery period (17.5 versus 32.2 days, $P = 0.0001$) and an earlier return to work (18.9 versus 49.7 days, $P = 0.005$).

In both groups the mortality rate was zero; the morbidity rates were similar (4.1 versus 3 per cent). In addition to the cosmetic and functional benefits of laparoscopic surgery and independent of late abdominal wall complications, which were not seen in this study, these results confirm all the socioeconomic benefits of this type of surgery, in the matter of hospitalization as well as time lost from work. This becomes essential in public health matters when dealing with a disease that affects a large segment of the population and that responds to a surgical treatment that is performed more than 80 000 times a year in France.

Laparoscopic cholecystectomy for complicated acute cholecystitis

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Acute cholecystitis and empyema are generally considered to be contraindications to laparoscopic cholecystectomy¹. Between May 1990 and October 1991 a total of 350 consecutive patients underwent laparoscopic cholecystectomy in our hospital with five conversions to open surgery. Of these, 31 had complicated acute gallbladder disease requiring emergency operation within 72 h of presentation. Twenty had an empyema, three of which had perforated, and ten had severe cholecystitis with transmural inflammation or gangrene, one of which had perforated. The operative technique was that used for elective laparoscopic cholecystectomy but deliberate gallbladder puncture was used in ten cases, modified retraction in five and retrograde dissection in two. Operation time was similar to that for elective surgery (90 min).

Two cases were converted because of severe inflammation precluding identification of the biliary anatomy. There was no operative mortality and morbidity was minimal. One of the patients converted to open operation developed urinary retention and there was one wound infection in the laparoscopic group. Patients who had emergency laparoscopic cholecystectomy required a median post-operative stay of 2 (range 1–6) days and regained normal activity in 7 (range 2–21) days.

Emergency laparoscopic cholecystectomy is a safe and effective treatment for complicated acute cholecystitis. It has a low morbidity rate, takes no longer than elective laparoscopic surgery and confers similar benefits to the patient.

1. Cuschieri A, Dubois F, Mouiel J *et al.* The European experience with laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 385–7.

Laparoscopic cholecystectomy: the Belgian registry

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The results of laparoscopic cholecystectomy as carried out currently by general surgeons have been prospectively investigated in an anonymous multicentre Belgian study, including 3244 patients operated on by 68 different surgeons. The results break down as follows: 15 per cent were older than 70 years; 48 per cent had had previous abdominal surgery; 5.4 per cent were classified grade III in the American Society of Anaesthesiology (ASA) classification; 77 per cent had uncomplicated gallstones whereas 13 per cent presented with acute cholecystitis and 9.8 per cent with a history of stone migration; 49 per cent were operated on by a surgeon with experience of less than 50 cases of laparoscopy. A conversion to laparotomy was required in 6.5 per cent of the patients, statistically related to the presence of acute cholecystitis, common bile duct stones, bile duct injury and laparoscopic experience of the surgeon. The mean postoperative hospital stay was 3.86 days for successful laparoscopic cholecystectomy and 9.55 days for patients converted to laparotomy. Hospital mortality rate was 0.2 per cent, including 0.1 per cent of technical mortality (related to biliary tract injury and haemorrhage). Overall postoperative complication rate was 6.4 per cent, comprising 2.3 per cent of general complications and 4.1 per cent of local complications. Non-biliary local complications occurred in 2.3 per cent (related to haemorrhage or infection) and biliary complications in 1.4 per cent including 0.5 per cent of bile duct injury and 1 per cent of biliary leak (spontaneously resolved in 80 per cent). Reintervention was necessary in 0.5 per cent of patients, related to biliary fistula, haemorrhage or abscess. Residual common bile duct stones occurred in 0.5 per cent of patients and were treated by postoperative endoscopic sphincterotomy.

In conclusion, even in the current practice of general surgeons, laparoscopic cholecystectomy is a safe procedure, essentially providing functional benefit to the patients. Adequate selection of the patients, selective conversion to laparotomy in difficult cases and inclusion of laparoscopy in surgical training are imperative to avoid unnecessary local complications.

Development of steerable instruments for minimally invasive surgery in modular conception

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One of the principle difficulties in complex endoscopic manipulations of internal organs, as are necessary in laparoscopic gastric surgery or endoscopic sigmoid resection, is the restricted degree of freedom of current endosurgical instruments. Usually torsion and rotation around their longitudinal axis and motion in the access channel are possible (i.e. two or three degrees of freedom). Our aim was the development of steerable instruments to enhance the operative capability of the surgeon. The first prototype (steerable minimally invasive surgery (MIS) instrument, SMI) is a grasper with two additional degrees of freedom; with a seven-joint multiknuckle working as the 'elbow' of the instrument, inclination (280°) of the effector is possible, as well as rotation around the axis. The instrument functions along the lines of a mechanical remote control handgrip. The movement is achieved by cables which are carried within the shaft. The internal flexible rod transmits both the tip's rotation and the movement of the jaws. This prototype has been tested in a simulator and in animal experiments (sheep and pigs) for laparoscopic and thoracoscopic interventions and shows a clear improvement of complex manipulations, such as the mobilization of internal organs and grasping structures. To define the requirements for optimized cinematic analysis of different MIS interventions, with reference to the range, the time required and the combination of the use of the instruments has been performed. To evaluate mechanical demands, the power used for the manipulation of the tissue was measured during operation with forceps having integrated sensors. The further development of steerable instruments is currently performed in a modular conception. The instrument represents a system of three different modules: the flexible steerable part, the rigid shaft and the control unit. The first mechanically controlled prototype of this modular flexible MIS-instrument (MFM) is being

evaluated. For each of the three parts of the modular systems different versions have been and will be developed including different types of links, joints and control units, to test a variety of combinations to determine the best adapted instrument for the use in MIS. The next MFM prototype (electrically driven) is currently being studied in simulators.

Coagulation, aspiration, irrigation and cutting combined in a single instrument

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In minimally invasive surgery, coagulation, aspiration and cutting are all required. When dissecting adhesions or a pedicle, coagulation with forceps is followed by transection with scissors. The changing of long instruments required is inconvenient and time consuming. Precise cutting of tissue in the dissecting zone is difficult, and if bleeding occurs another instrument is required to localize the source of bleeding by suction and irrigation.

To make this technique easier we have developed certain combination instruments for laparoscopic and endoscopic use. These are: a diathermy-suction-irrigation probe with an enlarged channel for instrument introduction (the irrigation channel is separately integrated); a suction probe with removable high-frequency dissecting hook; a bipolar coagulation forceps with water rinsing and instrumentation channel, mainly for use with scissors; a bipolar coagulation forceps with integrated cutting and irrigation function and central aspiration channel; and a bipolar coagulation forceps with irrigation and integrated movable scissors which also has a suction channel.

The instruments were designed and constructed by the authors in cooperation with Wolf, Knittlingen, Germany and the Nuclear Research Centre, Karlsruhe, Germany. We have tried and tested the instruments in simulators and in animals. The suction irrigation probe is now in clinical use.

Laser-induced thermotherapy and results of oncological surgery

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Laser surgery, in some applications, gives new technical opportunities to the surgeon and shorter postoperative courses to the patients. Significant differences in the rate and the outcome of local recurrences in animal mammary carcinoma models have been reported using carbon dioxide (CO₂) laser *versus* conventional resection¹. These facts led us to propose to surgeons performing oncological surgery with or without lasers an intraoperative protocol aimed at the destruction of potential residual cancer cells after surgical dissection. In *in vitro* experiments we have demonstrated the feasibility of obtaining a homogeneous thermal distribution of 50°C on a determined tissue area by defocused scanning CO₂ laser irradiation².

A group of 18 patients underwent treatment using a CO₂ laser, 125-mm handpiece, 5–7 cm from the target, 70–125 W cm⁻², scanning speed 2 cm s⁻¹. The laser irradiation followed resections of breast, renal, rectal and pleural carcinoma. The series included patients with staging T₁–T₄, N₀–N₊, M₀–M₊.

Results show no evidence of disease in 13 patients. The follow-up is 23–52 months. The failures concern rectal carcinoma: three of five patients had synchronous liver metastases. The satisfactory results concern breast and pleural tumours.

Intraoperative laser-induced thermotherapy is a safe method, not time-consuming and may become a way of controlling the intraoperative spread of malignant cells. Multicentre studies should be discussed as well as comparison with intraoperative radiotherapy techniques.

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2. Akoum H, Sultan RA, Gautherie M. Hyperthermia and the CO₂ laser: an experimental study. *J Clin Laser Med Surg* 1990; 8: 43–6.

Photodynamic therapy of pancreatic cancer in the rat

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The aim of this work was to test the efficacy of photodynamic therapy (PDT) on experimental pancreatic cancer. The tumour system was an acinar pancreatic cancer induced by azaserine and transplanted in the pancreatic tail of Lewis rats. The survival time of this model does not exceed 33 days. The photosensitizer used was pheophorbide A (PP-A), a chlorophyll derivative. The excitation sources were: (1) a 'Q-switched' neodymium yttrium-aluminium-garnet (NdYAG) laser (without thermic effect) at 1060 nm with 0.6 J pulse⁻¹ for 15 min (power density of 200 J cm⁻²); (2) a halogen light (200 W for 30 min).

Two groups of eight animals received either PDT (PP-A, 3 mg kg⁻¹ + NdYAG) or NdYAG laser alone (controls). Haemorrhagic suffusion of the tumours was observed during light exposure in the PDT group only. A major reduction of tumour size has been found at time of sampling in the PDT group. Histologically, the number and the volume of neoplastic acini were drastically reduced. Mitoses were rare and strong stromal fibrosis with numerous macrophages was observed. No specific changes were observed in controls.

The ratio of PP-A concentration between tumour and normal pancreas was 5:1 24 h after administration of the dye at a dose of 3 mg kg⁻¹ and 1.5:1 at a dose of 9 mg kg⁻¹.

Two groups of eight rats bearing a tumour <1 cm in diameter and receiving intravenous 9 mg kg⁻¹ of PP-A were treated respectively by NdYAG laser or halogen light. Control groups were treated only with PP-A, or NdYAG or halogen light alone. No significant

difference in actuarial survival was found between NdYAG + PP-A-treated group and control groups. The 1-month rate of survival was significantly different (50 per cent *versus* 12 per cent, $P < 0.05$). With halogen stimulation, both actuarial survival (log rank test, $P < 0.01$) and rate of survival (75 *versus* 12 per cent, $P < 0.001$, χ^2 test) were significantly different. Of the halogen treated animals, 50 per cent survived up to 45 days while all the controls were dead within 31 days after tumour transplantation. One animal remained alive up to 4 months after tumour transplantation.

At the present time surgical resection is the sole chance of cure in pancreatic cancer but for only 5 per cent of patients. Efficiency of surgical resection might be enhanced by adjuvant intraoperative photodynamic treatment.

Intraoperative laser-induced thermotherapy in oncological surgery

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Although laser oncological open surgery, in certain situations, gives technical advantages to the surgeon and shorter postoperative course to the patients, increased survival has not been shown. However, significant differences in the rate and the outcome of local recurrences in an animal mammary carcinoma model have been reported using carbon dioxide laser *versus* conventional resections¹. These observations led us to put forward to surgeons performing oncological surgery, with or without lasers, an intraoperative protocol aimed at destruction of potential residual cancer cells after surgical resection. In experiments *in vitro* we have demonstrated the feasibility of obtaining a homogenous thermal distribution of 50°C on a determined tissue area by defocused scanning carbon dioxide laser irradiation².

To date, 18 patients have undergone this protocol (carbon dioxide laser, 125-mm handpiece, 5–7 cm from the target, 70–125 W cm⁻², scanning speed 20 mm s⁻¹). The laser irradiation followed resection of breast, renal, rectal and pleural malignancies. The series includes patients with staging T₁–T₄, N₀–N₊, M₀–M₊.

No evidence of residual or recurrent disease was seen in 13 patients. The follow-up ranged from 23 to 52 months. The failures occurred with rectal cancer: three of five patients had synchronous liver metastases. Satisfactory results were seen for breast and pleural tumours.

Intraoperative laser-induced thermotherapy is safe and rapid. It may help to control intraoperative malignant cell spread. Multicentre studies as well as comparison with intraoperative radiotherapy should be considered.

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Laser angioplasty of peripheral vessels

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From February 1988 to April 1991, 46 thermal laser angioplasty procedures were performed on 35 patients using an argon laser (before February 1989) and a neodymium yttrium-aluminium-garnet (NdYAG) laser thereafter. In 40 cases a surgical approach and in six a percutaneous approach was taken to the lesions. After laser recanalization, traditional balloon angioplasty was performed to achieve an adequate arterial calibre. The operative success in relation to the length of the treated lesions was 95 per cent in lesions <10 cm and 66 per cent in lesions >10 cm. Patients were followed for 1–24 months: long-term patency rate in relation to length was 83 and 39 per cent respectively. The incidence of main complications was evaluated.

Microanastomosis by suture and laser: an experimental study

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The objective of this study was to compare carbon dioxide laser-assisted microvascular anastomosis with conventional sutured anastomosis.

The healing pattern, the tensile strength and the bursting pressure of conventional, laser-assisted and pure lasered anastomoses were compared in 192 Wistar rats. The anastomoses were carried out on the carotid artery and the vena cava. A 100-mW carbon dioxide laser was used. The rats were anaesthetized with ketamine, xylazine and atropine. Microscopic and immunofluorescence investigations, measurement of the tensile strength and the bursting pressure and radiological investigations were performed from 1 h up to 90 days after experiment.

Of the 192 rats, 28 died in the postoperative period; 14 rats died because of bleeding from pure lasered anastomoses, the others from pneumonia. Anastomoses of the arteries exhibited a similar reaction pattern with laser-assisted or conventional sutures. Pure lasered anastomoses had an unstable healing zone. Arterial dehiscences at the cut borders were observed after 7 days. There was no difference between conventional and laser-assisted techniques in the amount of small luminal thrombi.

Laser-assisted anastomoses had an immediate mean(s.d.) tensile strength of 28(3) g. After 7 days they reached a tensile strength of 45(5) g. After 90 days they reached the same strength as the conventional anastomoses. The laser-assisted anastomoses immediately resisted a mean(s.d.) bursting pressure up to 444(75) mmHg and after 7 days a bursting pressure of more than 600 mmHg. Pure lasered anastomoses were not strong enough to withstand bursting strength and tensile strength within physiological limits.

The present investigation supports the idea that the laser-assisted anastomosis is an advantageous technique in microsurgery; pure lasered anastomoses without stay sutures are not able to resist physiological values of bursting pressure and tensile strength.

Diagnosis, clinical relevance and pathology of the atrophy-hypertrophy complex of the liver

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A combination of atrophy and hypertrophy of the liver has been reported for many years and is nowadays recognized as the atrophy-hypertrophy complex (AHC). Biliary, portal, biliary-portal and hepatovenous obstruction have been recognized as the aetiological factors leading to AHC. The clinical significance of the phenomenon and the implications for surgical therapy are the subject of intensive research.

From 1987 to 1990 30 patients with documented significant AHC of the liver were treated. All patients were discussed at an interdisciplinary meeting of surgeons, gastroenterologists, radiologists and hepatologists, and were prospectively evaluated in respect of the aetiology and with regard to planning treatment. All patients were studied in detail, including clinical presentation, radiological and gastroenterological examinations, laboratory examinations, intraoperative findings and, in many cases, histological assessment.

The diagnostic pathway included ultrasonography in 29 patients, computed tomography in 26 patients, biliary and hepatic scintigraphy in 21 patients, endoscopic retrograde cholangiopancreatography in 14 patients, angiography in 14 patients and percutaneous transhepatic cholangiography (PTC) in eight patients. Aetiologically, a post-cholecystectomy stricture was found in 12 patients, a tumour obstruction in nine patients, and a variety of different aetiologies in five patients (*Echinococcus*, Budd-Chiari, primary biliary cirrhosis, Mirizzi syndrome). In four patients a unique aetiology could not be defined. On the basis of the histological studies, a new, prognostically relevant, histological classification of the AHC is presented. Severe histological changes generally imply a worse prognosis, even in benign diseases.

The clinical importance for therapy and prognosis is emphasized. The planning of therapy is always dependent on a precise diagnostic pathway. The early detection of AHC is essential for the planning of operative or non-operative therapy.

Laparoscopic treatment of non-parasitic liver cysts and polycystic disease of the liver

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During an 18-month period, two patients with non-parasitic cysts of the liver and seven patients with polycystic liver disease were treated by laparoscopic fenestration (Lin's procedure). The mean age of these female patients was 45.5 years. Three patients had had previous abdominal surgery and in four patients the polycystic liver disease had previously been treated by percutaneous aspiration ($n = 3$) or surgical fenestration ($n = 1$). Indication for surgery was painful hepatomegaly in all patients. Preoperative liver investigations included ultrasonography and computed tomography (CT) in all patients. Liver cysts were single in two patients and multiple in seven. Large cysts (>10 cm) were present in eight patients. Surgical fenestration with cyst wall excision was performed in all patients, with fenestration of renal cysts in one patient. Conversion to laparotomy was necessary in two patients, for a deep intrahepatic cyst in one case and for haemorrhage in a patient with diffuse multiple small cysts. The mean duration of pneumoperitoneum in successful laparoscopy was 107 (range 50–164) min. One postoperative complication occurred: a right pleural effusion in one patient who required conversion to laparotomy. The mean postoperative hospital stay in successful laparoscopic fenestration was 3.8 days. The postoperative follow-up time was 7.3 months: five patients were free of symptoms and two complained of abdominal pain related to spastic colon. Postoperative CT showed good results in four patients, was unchanged in one and showed recurrence of a single liver cyst in a patient treated by incomplete fenestration.

In conclusion, laparoscopic treatment of liver cysts is a safe surgical procedure. The best indication remains large, superficial and accessible liver cysts. Treatment included wide cyst wall excision to avoid recurrence.

Hepatocellular carcinoma in genetic haemochromatosis

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From 1975 to 1990, 51 patients presenting with hepatocellular carcinoma (HCC) as a complication of genetic haemochromatosis (GH) were seen at this institution. Twenty-one patients underwent laparotomy. This group was composed of 20 men and one woman, with a mean age of 62 years. The diagnosis of GH was made simultaneously with that of HCC in seven cases and preceded the diagnosis of HCC by a mean of 10 years in 14 other patients. High alcohol intake (>100 g day⁻¹) was found in seven patients. Surgical management was limited to exploratory laparotomy or surgical palliation in eight instances in which the tumour was deemed irresectable. Usually, these were patients presenting with diffuse lesions, operated on before 1985, at a time when resections for HCC in cirrhotic livers were not attempted. Thirteen patients underwent a partial hepatectomy (11 patients) or total hepatectomy with liver transplantation (two). The actuarial survival rate at 1 year for patients after liver resection was 56 per cent compared with 29 per cent for those having exploratory laparotomy or surgical palliation.

Analysis of these patients has enabled us to identify various risk factors for development of HCC in patients with GH. These are male sex, age over 60 years, history of GH of over 10 years, grade III or IV hepatic fibrosis, and high alcohol consumption. There appears, however, to be no relationship with the degree of iron saturation in liver parenchyma at the time of diagnosis.

Our experience with hepatic resections in cirrhotic livers (43 patients) has shown that these may be performed with a low operative mortality rate (6 per cent). Moreover, the actuarial survival rate at 3 years, after resection in patients with HCC secondary to GH, is as high as 40 per cent. Therefore we believe that, in view of the present shortage of liver organ donors, hepatic resection is the treatment of choice for these patients.

Hepatic resection for hepatocellular carcinoma

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During the past decade, 36 patients with hepatocellular carcinoma (HCC) were treated by hepatic resection. There were 11 women and 25 men, within an age range of 17–82 (mean 60) years. HCC was associated with liver cirrhosis in 16 patients.

The type of resection was a major hepatectomy (right lobectomy, left or right trisegmentectomy) in 16 cases, a partial hepatectomy (one or two segmentectomies) in 18 cases and in two cases a single wedge resection.

All patients underwent elective surgery, except for one suffering from spontaneous tumour rupture. This patient died immediately after operation. Of the other 35, three died in the postoperative period. The postoperative course was complicated in 22 patients. Of the 32 remaining patients, 13 died from tumour recurrence 4–36 months after resection; 14 patients are still alive without apparent recurrence, five of them at least 3 years after surgery. Of the five other patients, two are alive with recurrence, one died free from disease, and two have been lost to follow-up.

This study suggests that long-term survival can be achieved after surgical resection for HCC with or without associated liver cirrhosis.

Percutaneous ethanol injection in the treatment of hepatocellular carcinoma

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Percutaneous ethanol injection (PEI) under ultrasonographic guidance represents a real alternative to surgery in the treatment of hepatocellular carcinoma (HCC). Between September 1989 and June

1991, PEI was performed in 24 patients affected by HCC in cirrhotic livers, including two patients with postsurgical recurrence. The pretreatment workup included sonography, computed tomography and serum α -fetoprotein (α -FP) assay. The prothrombin time, partial thromboplastin time and platelet count were routinely measured before therapy. A group of 16 patients had a single tumour, six patients two lesions and two patients three. Sizes ranged from 8 to 70 mm in diameter. All HCCs were confirmed by sonographically guided fine needle biopsy (FNB). Six patients developed further lesions during treatment or during follow-up. Ultrasonographic and α -FP measurement were repeated every 3 months and computed tomography every 6 months.

Only one major complication was observed (a mild haemo-peritoneum treated with medical therapy). Mild to moderate fever of a few days duration, transient elevation of serum transaminases and bilirubin levels were noted. No systemic effects due to alcohol reabsorption were observed. After two or three injections, structural changes were noted in all cases by ultrasonography and the margins of the lesions became indistinct. At the end of therapy α -FP levels were significantly reduced (400 versus 105 ng ml⁻¹, $P < 0.05$). One- and 2-year overall survival rates were respectively 100 per cent and 80 per cent; 2-year survival rate in patients with single lesions < 5 cm was 100 per cent.

We agree that surgical resection remains the treatment of choice for HCC. Many patients however are poor candidates for surgery because of poor liver reserve resulting from coexisting cirrhosis. Our experience confirms that PEI is an easy, rapid, cheap procedure which can be safely performed in patients with cirrhosis affected by HCC. It represents a real alternative to surgery in the treatment of this condition.

Primary cancers of the liver in children: combined treatment with extended resection and chemotherapy

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Between 1977 and 1991, 23 children were treated for primary cancer of the liver. Hepatoblastoma was present in 12 patients of median age 9 (range 3–46) months. Surgical resection involved seven trisegmentectomies (six right and one left), three bisegmentectomies (two right and one left) and two left segmentectomies (US terminology), without operative mortality. Major complications included one bile leak corrected by a Roux-en-Y loop and one Budd–Chiari syndrome due to unsuspected thrombosis of the remaining left hepatic vein which was successfully corrected by *in vivo*, *ex situ* resection and reimplantation. Four patients had no preoperative chemotherapy with three recurrences and two deaths; the fourth patient is alive and disease free with a follow-up of 12 years. The other nine patients had a full course of preoperative chemotherapy (cisplatin–Adriamycin); all are alive and disease free with a median follow-up of 25 (range 2–48) months.

Hepatocellular carcinoma was present in seven patients of median age 99 (range 30–162) months. Surgical resection involved two trisegmentectomies (one right and one left), one right bisegmentectomy and four total hepatectomies (two with metabolic disease) with orthotopic liver transplantation (OLT) without operative mortality or major complications. One patient died from recurrence 8 months after OLT following three successive partial resections without chemotherapy. Three patients are alive and disease free 1–27 months after partial resection combined with chemotherapy, as well as the three remaining patients after total hepatectomy and OLT combined with chemotherapy (follow-up of 2–56 months).

Other tumours present in four patients were treated by partial resection, for a fibrosarcoma or rhabdomyosarcoma (two), or by total hepatectomy and OLT for an angiosarcoma (two). Only one is alive after chemotherapy and partial resection for a rhabdomyosarcoma.

In conclusion, our experience confirms that in primary cancer of the liver, extended resection with chemotherapy is possible without therapy-related disease and with a high potential of cure.

Factors influencing tumour recurrence after resection of hepatocellular carcinoma in the cirrhotic liver

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In the past 4 years, 33 hepatic resections for hepatocellular carcinoma have been performed in 31 patients with liver cirrhosis in our unit. The mean (s.d.) age of the patients was 63(7) years. The aetiology of the liver cirrhosis was alcohol abuse in eight cases, postnecrotic in 15 and other causes in eight. Serology for hepatitis C was positive in 55 per cent of patients. The mean (s.d.) tumour size was 4.4(2.9) cm. Most patients were treated with limited resection. Operative mortality rate was 13 per cent. Follow-up ranged from 2 to 47 (mean 16(12)) months. Tumour recurrence was diagnosed in 59 per cent of the survivors: four distant metastases and 12 intrahepatic recurrences (six adjacent to resected segments, four in a distant segment and two multiple or diffuse recurrences). Nine recurrences were found within the first year and seven after 1 year. Two patients were reoperated on in order to resect a nodular recurrence.

Demographic and pathological characteristics of cirrhosis and hepatocellular carcinoma were studied to analyse the risk of recurrence. Hepatitis B cirrhosis, macronodular cirrhosis, non-trabecular and undifferentiated tumour, tumour size > 3 cm, presence of satellites or more than one nodule and vascular invasion were associated with a higher incidence of recurrence. Overall survival rate was 48 per cent and actuarial survival rates at 1 and 3 years were 69 per cent and 32 per cent.

In conclusion, the rate of recurrence of hepatocellular carcinoma in cirrhotic patients is high with surgical resection alone.

Relevance of computed tomography in the conservative management of blunt liver trauma

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Increasing experience with early radiological evaluation (ultrasonography (US) and computed tomography (CT)) of patients with abdominal trauma results in the more frequent use of conservative treatment in patients with severe liver injuries. In a retrospective study, three of 100 patients with liver injuries diagnosed mainly by peritoneal lavage were treated non-operatively. In a consecutive, prospectively evaluated series of 80 patients with early use of US and CT for diagnosis, 30 patients in stable circulatory conditions were treated non-operatively. With increasing experience, a higher percentage of patients, even with severe liver injuries, could be treated without operation.

Although a precise anatomical classification of the degree of liver injury (modified after Moore) seems difficult, the predictive value of CT for non-operative treatment was good. Use of intravenous contrast is mandatory.

In the overall group of 80 prospectively evaluated patients with early US and CT, 17 patients with minor injuries (estimated grades I and II) and 13 patients with severe injuries (estimated grades III and IV) could be treated without operation. Three patients initially allocated to non-operative treatment had to be operated on within 10–72 h because of secondary bleeding and/or necrosis and devitalized liver tissue. Two patients with a grade IV injury developed an arteriovenous fistula and an aneurysm which necessitated embolization. All conservatively treated patients have been followed up for a mean of 9 months without complications.

It is concluded that in experienced hands CT allows a precise evaluation of liver injuries. This may permit non-operative treatment, provided there is careful clinical evaluation of circulatory stability.

Hepatic flow scintigraphy in the evaluation of hepatic metastasis in patients with gastrointestinal malignancy

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Ultrasonography and computed tomography are unable to detect accurately hepatic metastases < 1.2 cm in diameter. This detection

has become of greater importance with the development of techniques for their successful resection, and the evaluation of intraportal or intraperitoneal chemotherapy.

Hepatic flow and static scintigraphy (3 mCi technetium-99m) have been carried out in 129 patients undergoing surgery for gastrointestinal cancer. Metastases were identified at laparotomy in 15 of the 129 patients. Of the 114 patients without metastases at laparotomy, 13 have shown evidence of developing overt metachronous hepatic metastases with a follow-up of 2 years or more.

For the detection of synchronous hepatic metastases the sensitivity of hepatic flow (limit range 0-42) and static scintigraphy was 73 per cent and 80 per cent, respectively, and the specificity was 69 per cent and 40 per cent. For metachronous hepatic metastases, the sensitivity and specificity of the hepatic flow were 92 per cent and 66 per cent, respectively. The positive and negative predictive values were 15 per cent and 97 per cent, respectively.

If adjuvant chemotherapy can reduce the incidence of metachronous liver metastases, the high negative predictive value of hepatic flow scintigraphy could be used to avoid this treatment in one-third of the patients in this series.

Haemofiltration and haemodialysis during intra-arterial infusion of high-dose mitomycin in patients with liver metastases from colorectal cancer

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A phase 1 study has been performed in patients with liver metastases from colorectal cancer to evaluate the effectiveness of drug removal techniques in high-dose locoregional chemotherapy.

Twelve patients with synchronous or metachronous multiple bilobar liver metastases from colorectal cancer were studied. Haemofiltration and haemodialysis of suprahepatic venous blood were performed during repeated intra-arterial infusions of high-dose mitomycin (30 mg m^{-2}). Drug concentrations were measured both in the extracorporeal circuit and in blood samples taken to evaluate the effectiveness of the drug removal techniques.

Using haemofiltration, the reduction in mitomycin bioavailability was 20-60 per cent in the extracorporeal circuit and 14-40 per cent in patient blood samples. With haemofiltration and haemodialysis the reduction in mitomycin bioavailability was 49-75 per cent in the extracorporeal circuit and 20-55 per cent in patient blood samples. No immediate toxicity was observed in any patient. Mild late haematological toxicity was observed in three patients. Response estimated by computed tomography or nuclear magnetic resonance was one complete response (8 per cent), six partial responses (50 per cent), three with no change (25 per cent) and two with progressive disease (17 per cent). Four patients died, with a mean survival after treatment of 4 months. Eight patients are alive, with a mean survival of 15 months.

Haemofiltration and haemodialysis together allowed better mitomycin total body clearance after high-dose intra-arterial infusion than haemofiltration alone.

Combined treatment of irresectable liver metastases of colorectal cancer by chemotherapy and subsequent hepatic resection

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Hepatic resection is known to be the sole curative treatment of liver metastases from colorectal cancer but is used for fewer than 10 per cent of patients. When the liver metastases were irresectable, a circadian rhythm modulated chemotherapy was used to optimize dose intensities and drug tolerance. The aim of this treatment was to achieve tumour reduction and to allow, when possible, a subsequent liver resection. From October 1986 to November 1990, 65 patients with irresectable liver metastases of colorectal origin were treated by intravenous chronomodulated chemotherapy. 5-Fluorouracil (5-FU ; $700 \text{ mg m}^{-2} \text{ day}^{-1}$) and folinic acid (Fol; $300 \text{ mg m}^{-2} \text{ day}^{-1}$) combined with oxaliplatin (1-OHP, a non-nephrotoxic platinum complex; $25 \text{ mg m}^{-2} \text{ day}^{-1}$) were continuously infused for 5 days

every 3 weeks. Drug delivery was sinusoidally modulated along the 24-h scale with peak flow rates at 04.00 hours for 5-FU and Fol and at 16.00 hours for 1-OHP using an ambulatory programmable-in-time pump. All the patients had cancer initially considered as irresectable by the same surgical team and were subsequently re-evaluated for resection.

The results are shown in the Table.

	n	Response (%)	Resection (n (%))	1-Year survival rate (%)	2-Year survival rate (%)
Total group	65	60	12 (18)	66	33
Group 1 (liver)	32	53	8 (25)	65	54
<50% involvement	17	88	8 (47)	84	70
>50% involvement	15	20	0 (0)	37	37
Group 2 (liver + others)	33	67	4 (12)	68	16

Of the 12 patients who underwent subsequent resection, six had additional resection of extrahepatic tumours (lung three, peritoneum two, kidney one) and six subsequently underwent a second liver resection for recurrence. Of all resected patients, one died of recurrence at 27 months, two are alive with recurrence at 21 and 23 months and nine are alive without recurrence at respectively 16, 16, 16, 17, 20, 24, 31, 37 and 37 months.

It is concluded that: (1) modulated intravenous chemotherapy using this chronopharmacological protocol has a 60 per cent objective response rate which allowed a second-step liver resection in some patients initially considered as irresectable; (2) a clear survival benefit may be expected for such patients on the basis of this combined approach.

Long-term survival and prognostic factors of treatment of hepatic metastases of colorectal cancer

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The aim of this study was to report the long-term survival and to analyse prognostic factors influencing survival of 49 (34 men and 15 women, mean age 59.3 years) patients treated for hepatic metastases from colorectal cancer. Twenty-nine patients had synchronous liver metastases, while 20 had metachronous liver metastases. The stage of hepatic disease was assessed using the Gennari classification: 12 patients had stage I liver disease, nine stage II, 18 stage III and ten stage IV. Patients were divided into three groups according to the treatment performed: group A consisted of 12 patients who underwent surgical excision of the metastases; group B comprised 14 patients who underwent surgery and locoregional chemotherapy; and group C comprised 23 patients treated by hepatic arterial chemotherapy. In all patients, locoregional chemotherapy was performed using totally implantable infusion systems with the catheter inserted in the hepatic artery via the gastroduodenal artery. Mean survival was 34.7 months in group A, 21.5 months in group B and 13.1 months in group C. Multivariate analysis of prognostic factors showed that the only variables that statistically influenced survival were the stage of hepatic metastases ($P < 0.0001$) and disease-free interval ($P < 0.006$).

Focal nodular hyperplasia: resection in 20 patients

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From 1980 to 1991, 20 patients underwent liver resection for lesions that were diagnosed as focal nodular hyperplasia (FNH) at pathological examination. The group comprised three men and 17 women with a mean age of 37 (range 19-57) years. Nine women had taken oral contraceptives for an average of 8 years.

In five instances surgery was performed for an unrelated pathology (megaesophagus, cholecystitis, perforated duodenal ulcer, colonic metastases and hepatocellular carcinoma) and FNH was a chance finding. Among the remaining patients ($n = 15$),

preoperative tests correctly identified FNH in only two cases (13 per cent). Other likely diagnoses were hepatic adenoma ($n = 6$), malignant lesion ($n = 3$) or uncertain ($n = 4$). Despite convincing evidence in favour of FNH, two women of child-bearing age underwent liver resection because of right upper quadrant pain.

Patient work-up comprised serum α -fetoprotein levels ($n = 12$), abdominal ultrasonography ($n = 17$), computed tomography ($n = 13$), arteriography ($n = 4$), nuclear magnetic resonance imaging ($n = 4$) and scintigraphy ($n = 5$). Surgical procedures comprised tumorectomy ($n = 11$), segmentectomy ($n = 1$), left lobectomy ($n = 4$), right hepatectomy ($n = 3$) and extended left hepatectomy ($n = 1$). At pathological examination average tumour size was 6.6 cm and tumours were always solitary. Women taking oral contraceptives had significantly larger lesions. Associated lesions included a hepatocellular carcinoma, liver lymphoma, colonic metastasis and haemangioma in one case each. Liver cirrhosis was never present.

There was no operative mortality or morbidity and mean hospital stay was 8 (range 6–12) days. Average follow-up is 42 months. One patient died at 6 months from a lymphoma. Among a group of six patients in which abdominal pain could not be attributed to another pathology and who underwent liver resection for FNH, two have had recurrence of abdominal pain.

FNH commonly presents as a solitary lesion in women of child-bearing age. Our results indicate that oral contraceptives, while not increasing the incidence of FNH, are however responsible for an increase in the size of lesions, which consequently become symptomatic. Furthermore, despite recent progress, positive diagnosis of FNH by imaging techniques alone is seldom achieved. Many lesions still require biopsy or removal to establish diagnosis. Finally, we recommend circumspection before considering resection for relief of abdominal pain in women with lesions which are probably FNH.

Graded augmentation of blood flow to the liver: a microsurgical technique and model

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An augmented blood flow model to the liver provides a useful means of studying the response of this organ in various experimental manipulations. The aim of this study was to create a surgical shunt between the vena cava (IVC) and portal vein (PV) in an effort to control the amount of blood presented to the liver through the shunt.

Wistar rats of either sex (250–360 g) were given (a) total caval portal shunt (CPS); (b) split CPS; or (c) split CPS plus an arteriovenous fistula (AVF) between the aorta and IVC. A preliminary minimal dissection of the IVC (between the liver and the left renal vein (RV)) and PV was done in all rats. A total CPS was made by ligating the IVC at the liver, clamping the proximal IVC above the right RV, dividing the IVC below the ligature and anastomosing it to the PV end-to-side using vascular control and microsurgical technique. For a split CPS, the IVC was clamped proximal to the IVC–left RV junction, ligated and divided just below the right RV and anastomosed in a similar manner to the PV, every effort being made to construct a high anastomosis. An AVF measuring 1 mm in diameter was made in the common wall between the aorta and IVC through a venotomy. This was added to the split CPS after the completion of a shunt.

Preliminary results revealed a >90 per cent success rate, functional shunts and the absence of a venacaval obstruction syndrome. The techniques described alter the quantity of blood flow to the liver, its oxygen status and its hormonal content. Notably, the endocrine secretions of the adrenal gland, kidney, testicle and ovary drain into the liver.

Selective accumulation of endogenously produced porphyrins in rat liver metastases: a new method of photosensitizing malignant tumours

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Porphyrins such as dihaematoporphyrin ether/ester (DHE) have been used successfully in photodynamic therapy of malignant tumours. Their application in liver tumours, however, has been

restricted, as more DHE accumulates in normal liver than in tumour. Neoplastic cells have higher porphobilinogen deaminase and lower ferrochelatase activities than normal cells. The possibility of making use of these differences in enzyme activities to cause selective porphyrin accumulation in tumours by administering the porphyrin precursor 5-aminolaevulinic acid (ALA) was therefore examined.

A piece (2 mm³) of syngeneic colon carcinoma CC531 was implanted in the liver of Wag/Rij rats. Groups of between five and eight rats were given ALA (2 mg ml⁻¹) in drinking water from the eighth, 14th or 17th day after tumour implantation. Two other groups received DHE intravenously, either 2.5 mg or 5 mg kg⁻¹ on day 17. On the 19th day after tumour implantation the livers were removed and porphyrin concentrations measured in normal liver and tumour by solvent extraction and high-pressure liquid chromatography.

Porphyrin (mainly protoporphyrin) accumulated progressively in the tumour with increasing duration of ALA administration, whereas no increase in porphyrin concentration was found in normal liver. After 11 days of ALA the porphyrin concentration ratio between tumour and liver was 4:1. In contrast, DHE concentration was higher in normal liver than in the tumour (tumour:liver ratio 1:3) after 5 mg DHE kg⁻¹.

In conclusion, oral administration of ALA results in the progressive accumulation of porphyrin in a transplantable colon carcinoma, without porphyrin accumulation in the surrounding tissue. The selective increase in porphyrin concentration in tumour tissue after oral ALA suggests that this may be a suitable approach to photosensitizing liver tumours or to early detection of tumours by fluorescence in ultraviolet light.

Experimental colorectal liver metastases in the rat: stimulation of dormant tumour cells by hepatectomy and cyclosporin A

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In recent years the interest in the development of experimental models of colorectal liver metastases has increased due to the need for new adjuvant therapies to improve the treatment of both colorectal cancer and metastases. Direct intraportal injection of cells derived from a colon carcinoma cell line is the most widely used experimental model.

The aim of this work was to evaluate whether intrahepatic recurrences observed after resection of colorectal liver metastases in humans could be due to the activation of cancer cells already present within the liver but which had remained dormant until liver resection. This hypothesis has been tested on an experimental model in the rat using intraportal cancer cell aggregates.

A total of 250 cell aggregates (DHDK12 colon carcinoma cell line) was injected into the portal vein of 70 BD IX rats. Eight weeks later, 43 rats with no apparent liver metastases were randomly divided into three groups: group 1 ($n = 15$) served as control; group 2 ($n = 15$) rats were given cyclosporin A (CsA) (10 mg per kg body-weight per day) for 28 days; group 3 ($n = 13$) rats underwent a 70 per cent hepatectomy.

When killed, 12 weeks after the injection of cells, 20 per cent of rats in group 1 had liver metastases, 80 per cent in group 2 ($P < 0.01$) and 61 per cent in group 3 ($P < 0.05$).

This model demonstrates the presence of cancer cells in the liver although no apparent metastases were observed at 8 weeks. It can be hypothesized that undetectable liver micrometastases were already present at 8 weeks and had not developed until stimulation by CsA immunosuppression or by liver regeneration following hepatectomy. In humans, a similar mechanism could explain some recurrences observed after resection of liver metastases. These experimental results could justify the testing of adjuvant therapies following partial liver resection for colorectal liver metastases in humans.

Hepatic perfusion index: an aid to the diagnosis of occult hepatic metastases

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Diagnosis of hepatic micrometastases is an unsolved problem in digestive surgical oncology. Hepatic Perfusion Index (HPI), the

relative hepatic arterial contribution to total liver blood flow, derived by dynamic hepatic scintigraphy (DHS)¹, has been suggested as a promising method in the definition of a high-risk group of patients prone to develop overt hepatic metastases after an apparently curative resection.

In this prospective study we attempted to evaluate the use and reproducibility of preoperative determination of an HPI in 147 patients with digestive cancer. A normal range with an upper limit of 0.28 was obtained in a group of 17 patients without neoplasia. Overt liver metastases were found in 34 patients undergoing laparotomy, and 26 (76 per cent) had elevated HPI values. No apparent hepatic metastases were found in the remaining 113 patients submitted to a 'curative' resection of the primary tumour; 64 had elevated HPI values. These patients were followed up by periodic clinical examination, hepatic ultrasonography and computed tomography. At 1 year of follow-up 64 patients were evaluated. Seven patients developed hepatic metastases; six of these patients had initial elevated HPI values and one had an initial normal value. Fifty-seven patients did not develop hepatic metastases; 36 had elevated initial HPI values and 28 had normal HPI values. These data result in a sensitivity of 76.9 per cent and a specificity of 43.3 per cent for DHS and a predictive value for a positive HPI of 16.7 per cent at 1 year, and a predictive value for negative HPI of 96.4 per cent.

These results show that, although initial elevated HPI values do not identify a high-risk group of patients prone to develop hepatic metastases, patients with initial normal HPI values have a confirmed low risk of developing hepatic metastases.

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Hepatic volume determination using three-dimensional computed tomography

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Resection of a hepatic carcinoma in the cirrhotic liver or an extensive hepatectomy in healthy tissue can be considered only if there is enough remaining hepatic volume to survive. Similarly, in liver transplantation it is important to know the recipient's liver volume in order to select the best sized graft. Ultrasonography and two-dimensional computed tomography (CT) provide poor estimates of liver volume. The aim of this study was to test the reliability of three-dimensional CT in measuring hepatic volume.

Eight livers were dissected from corpses. The reference liver volume was determined by water displacement. An Elscint 1800 scanner with Elscint software was used. Three protocols were tested: 10-mm sections every 10 mm, 5-mm sections every 5 mm, and 5-mm sections every 10 mm. The liver contour was automatically determined in every section by following isodensity lines. The computer then calculated the reconstructed volume.

Median (range) liver volumes were: displacement 1264 (868-1839) cm³; 10/10-mm sections: 1269 (849-1541) cm³; 5/5-mm sections: 1221 (860-1611) cm³; 5/10-mm sections: 1210 (859-1626) cm³. The correlation coefficient *r* with displacement volume was 0.93 (*P* < 0.001) for 5/5-mm three-dimensional CT sections, 0.92 (*P* < 0.001) for 10/10-mm and 0.94 (*P* < 0.0006) for 5/10 three-dimensional sections.

Three-dimensional CT is a good method for objective and precise determination of hepatic volume.

Experience in the treatment of hydatid cyst of the liver

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We present 10 years of experience with the treatment of liver hydatidosis between 1982 and 1991. In that period 74 patients were operated on for cystic echinococcosis of the liver.

The operative strategy depended on the intraoperative findings. Functioning liver parenchyma was spared whenever possible. The crucial points in the operative management are prevention of spilling and contamination and a meticulous search for communication between the bile ducts and the cyst.

For the first 4 years, the most frequently employed operative procedure was partial cystectomy with capitonnage (41 patients). In four cases the echinococcus of the liver perforating into the bile ducts was treated by removing the pericyst, cholecystectomy and T-tube drainage. In only two cases, one with a calcified cyst and one with a cyst on the periphery of the liver, was a total pericystectomy performed. In the past 6 years, after the partial pericystectomy an omentum flap was placed and fixed in the cavity of the pericyst and two drains placed in the cavity. This has been done in 27 cases. The incidence of postoperative complications was 11 per cent (eight patients). The operative mortality rate was 3 per cent (two patients).

We conclude that the method of choice in the treatment of hydatid disease of the liver is partial cystectomy, evacuation and sterilization of the cyst, visualization and closure of communicating bile duct and omentoplasty with drainage. In a series of 27 patients with liver hydatidosis treated by this method there was no mortality or morbidity after omental transposition, and mean hospitalization was 14 days.

Extraperitoneal drainage of the posthydatid residual cavity

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Experience is reported of external drainage of the posthydatid residual cavity via the extraperitoneal route using the round ligament method introduced by Professor D. Burlui. The clinical data include more than 200 drainage procedures accomplished in this manner; occasionally, double drainage was used. This method has proved effective and has the advantage of no peritubular losses. Regardless of the site of the residual cavity or of the type of surgery performed, the method may be used in any situation, either as definitive treatment or associated with cystointestinal anastomoses, with or without reduction of the cavity. The technique is simple and without risk. It offers effective drainage and definitive treatment, producing patient comfort and ease of nursing.

It is therefore recommended as being superior to direct drainage methods with rubber tubes or de Pezzer's catheters, which encourage the appearance of subphrenic and subhepatic abscesses.

Broad hepatopericystectomy with complete obliteration of the residual cavity in the surgery of hydatid cysts of the liver

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A total of 324 hydatid cysts of the liver underwent operation. In 245 operations a new procedure devised by the authors has been undertaken: broad hepatopericystectomy combined with complete obliteration of the residual cavity. Application of tincture of iodine and sulphonamide before suture of the residual cavity made it possible to operate even on pus-filled cysts (102 cases). Contrary to expectation, liver parenchymal damage was not observed after this. The favourable effects of this procedure are: (1) antiparasitic; (2) intense bactericide; and (3) scarring by irritation, generating adhesions which prevent recurrence.

Biliary drainage was most frequently performed by choledochoduodenostomy, external bile drainage proving sometimes to be inefficient. Reoperations were necessary in some externally drained cases.

Postoperative recovery was in general favourable and superior to that of other methods. Patient age ranged from 13 to 82 years. Mean duration of stay in hospital of these patients was 15 days. Mortality in the postoperative period was 1.8 per cent.

Operative risk of rehepatectomy for liver tumours

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Rehepatectomy for recurrent primary or secondary liver carcinomas has become more frequent. The purpose of this work was to assess the operative risk of rehepatectomy. Between 1984 and 1991, 295 liver resections were performed. Twenty-seven resections (9.2 per cent) were rehepatectomies: a second resection in 23 patients and a third resection in four patients. Sixteen patients were men and seven

women. Mean age was 53 (range 18–73) years. Ten patients had recurrent metastases from colorectal primaries, seven patients (six with cirrhosis) had recurrent hepatocellular carcinoma and six patients had other tumours. The first liver resection in these patients had been major resection in nine cases, segmentectomy (one or two segments) in ten cases and atypical resection in four. Rehepatectomy was major in seven patients, segmental in seven and atypical in 13. Operative mortality rate was 4.4 per cent (one patient). Mean (s.d.) operative blood transfusion was 4.5 (5.2) units of packed red cells, twice the mean blood transfusion in first-hand hepatectomies in our series. Four patients (14.8 per cent) had operative complications: thrombosis of portal vein requiring a portacaval shunt, injury to hepatic duct resulting in T tube drainage, and coagulation disorders with diffuse bleeding in two patients. The latter complication occurred in two of the four patients with a third liver resection. Bleeding stopped after packing in one patient with a normal liver. Bleeding resulted in death from exsanguination in the second patient, who had liver cirrhosis. Severe operative complications were more frequent in patients with a third hepatectomy (50 per cent) than in patients with a second hepatectomy (8.7 per cent).

These results suggest that the operative risk of rehepatectomy is far greater than that of a first liver resection. Third hepatectomies should be viewed with caution, particularly in patients with cirrhosis.

Hepatectomy with mechanical stapler: experimental results

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Carcinoma of the colon is the second most frequent tumour in humans and often at the time of presentation has already metastasized to the liver; hence there is a need for a technique that enables typical or atypical hepatectomy to be performed with ease, speed and reliability.

The suggested hepatic resection with the use of a mechanical stapler was studied in ten rabbits, followed up for 3 months. This technique showed effective haemostasis, so that in none of the experimental animals was there blood or biliary loss from the limit of the hepatic resection. Histologically, the signs were of regular and quick regeneration.

This technique was used in two cases of carcinoma of the colon with a single hepatic metastasis in the left lobe; the postoperative course was uneventful. We envisage the development of a device with specific characteristics for both the different segmentectomies and lobectomies, without preventive haemostasis. This will reduce the operation time, without blood and biliary loss.

Use of linear staples in liver surgery

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Our experience of the use of mechanical staples in hepatic resections is presented, and results obtained both experimentally and clinically are analysed. In the first experiment (on pigs), 15 hepatic resections were performed, achieving vascular ligation with linear vascular staples and liver section and haemostasis using linear polysorb staples. The use of staples allowed perfect sealing of the resection edges without secondary bleeding or biliary leakage. In the clinical group, ten major hepatic resections have been performed to date, with the same excellent result. This technique allows easier, quicker (and probably safer) surgery.

These results have been compared with those from 38 major hepatic resections performed by conventional surgical techniques. We believe this new technique represents a significant advance in liver surgery.

Oesophageal varices: role of the distal splenorenal shunt in the sclerotherapy era

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Sclerotherapy is now the first-choice treatment for bleeding oesophageal varices; several authors, therefore, question the value of portosystemic shunts, including the distal splenorenal (Warren) procedure.

From 1969 to 1991, 54 patients underwent splenorenal shunt after one or more oesophageal variceal haemorrhages. Sixty-day mortality was 15 per cent (eight deaths). Three patients were lost to follow-up soon after hospital discharge. The remaining 43 patients were followed for a mean of 5.2 years: 27 died, three were lost to follow-up and 13 are presently alive. Only four of the patients who were followed up suffered recurrent bleeding because of a thrombosed shunt. Temporary mental disturbances were noted in four cases but no incapacitating encephalopathy was recorded. In the last 10 years, the use of the Warren shunt has decreased strikingly as a result of the increasing popularity of endoscopic sclerotherapy. Surgical and anaesthetic techniques have, however, improved too, resulting in lower morbidity and mortality rates.

As recurrent bleeding and neurological sequelae are rare, we conclude that the distal splenorenal shunt remains a valuable alternative to long-term sclerotherapy in selected cases.

Highly selective devascularization for bleeding varices

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The early and late results of devascularization, the only major operation that has survived the shrinking role of surgery in oesophageal varices, are reviewed. The modified technique consists of devascularization of the upper two-thirds of the stomach and the lowest 7 cm of the oesophagus through a wholly abdominal approach. The greater curve devascularization is combined with splenectomy, and that of the lesser curve is done as in highly selective vagotomy but concentrating on the vessels. The operation is completed with partial fundoplication.

This study reports the results of 10 years of this operation during the period 1975–1984 in 419 cases; 126 were urgent and 293 elective. The overall urgent operative mortality rate was 8 per cent, and the elective mortality rate was 2 per cent. The recurrent bleeding rates in survivors were 8 per cent in 1 year, 15 per cent in 5 years, and 24 per cent in 10 years. The survival rates were 84 per cent for 1 year, 72 per cent for 5 years, and 57 per cent for 10 years. Recurrent bleeding was controlled usually by endoscopic sclerotherapy and less often by reoperation, which sometimes included stapling. Results in the second 5-year period (1980–1984) were significantly better than those in the first 5-year period (1975–1979).

As the operation for oesophageal varices must control the bleeding without further damaging hepatic function, we conclude that modified devascularization is the most suitable operation in our portal hypertension cases, both urgent and elective.

Mesocaval shunting for severe bleeding from oesophageal varices due to portal vein thrombosis secondary to protein C deficiency

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The 5-year-old second-born child of healthy parents was referred with severe haematemesis. There was no preceding history. On clinical examination the child looked pale with normal pulse and blood pressure but a tender epigastrium on palpation. He had a haemoglobin level of 9 g dl⁻¹ and a haematocrit of 27 per cent. Activated partial thromboplastin time, prothrombin time, fibrinogen as well as liver and renal function tests were within normal ranges. Oesophagogastroscopy revealed bleeding from oesophageal varices and from varices in the upper gastric area. Sclerotherapy of the bleeding varices was performed. Ultrasonography of the abdomen showed thrombosis of the portal vein with poor recanalization. After Sengstaken–Blakemore tube compression and somatostatin therapy, bleeding persisted and urgent surgical treatment became mandatory. At operation, the liver looked macroscopically normal and portal vein thrombosis was confirmed. With the use of an internal jugular vein graft a mesocaval shunt was constructed. Liver biopsy revealed only minor portoportal fibrosis. Six weeks after operation varices were still present endoscopically but duplex ultrasonography confirmed the functioning of the shunt. As there was no explanation for the portal thrombosis in the child's medical history a thorough investigation for disorders of coagulation was carried out. A protein

C deficiency was discovered with 37 per cent antigen and 40 per cent protein C activity. The protein S status was normal.

Protein C or protein S deficiency requires life-long therapy with oral anticoagulants for only this will prevent thrombotic events and, in this case, maintain shunt patency.

When bleeding from oesophageal varices cannot be controlled with conservative measures, surgery can be of help with mesocaval or other shunting procedures.

Calibrated portacaval shunt for haemorrhage in cirrhotics

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Encephalopathy is a major complication of portacaval shunt (PCS), due mainly to abolition of hepatic portal perfusion. To prevent this complication, calibrated PCS using polytetrafluoroethylene (PTFE) ringed prostheses has been performed to achieve a partial portal diversion while maintaining hepatic flow.

From September 1986 to October 1991, 31 patients (22 men and nine women) with confirmed cirrhosis and variceal bleeding have undergone a side-to-side calibrated PCS. The size of the shunt was 12 mm in four patients, 10 mm in 23 and 8 mm in four cases. According to a modified Pugh classification, 22 patients were grade A and nine were grade B. Cirrhosis was alcoholic in ten patients, posthepatic in 14 and due to other causes in seven patients. Most procedures (28 of 31) were performed electively after one or several episodes of variceal bleeding. Portal haemodynamics were assessed during the operation in each patient before and after shunting.

Operative mortality rate at 2 months was 3 per cent (one of 31); one patient died from rapid hepatic failure with graft thrombosis and variceal rebleeding 1.5 months after the shunt. No other patient experienced variceal rebleeding for a mean (range) follow-up of 25 (2–58) months. The mean (s.d.) reductions in portacaval pressure gradient were significantly related to the size of the graft: 36(10) per cent, 57(12) per cent and 63(11) per cent respectively for 8, 10 and 12 mm grafts ($P < 0.05$). An acute encephalopathy occurred in three patients (10 per cent) but no patient suffered from chronic encephalopathy. The patency of the shunt was routinely assessed in each patient by postoperative ultrasonography. On angiography at 1 year, portal perfusion was maintained in seven of ten patients receiving a 10-mm PCS. The 3-year survival rate is 88 per cent for the whole group, 95 per cent for patients of grade A and 67 per cent for patients of grade B.

We conclude that calibrated PCS may achieve partial portal diversion with maintenance of hepatic portal perfusion. The procedure is simple and efficient with a low operative mortality rate and a reduced risk of encephalopathy compared with conventional shunts. It is a valid alternative to sclerotherapy in patients who are not yet candidates for liver transplantation.

Portal obstruction: management and therapeutic implications

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Portal thrombosis (PT) is usually observed in cirrhosis and in pancreatic diseases. 'Idiopathic' PT is most often due to haematological disorders. The aim of this study was to evaluate the incidence, aetiology, specific treatment and surgical consequences of PT. PT with hepatocellular carcinoma and acute venous infarction was excluded.

From 1986 to 1991, 27 patients with thrombosis of the portal vein (PV), superior mesenteric vein (SMV) and/or splenic vein (SV) were studied. The patients were grouped as follows: (a) 12 (44 per cent) patients had liver cirrhosis, with thrombosis of PV ($n = 5$), associated with SMV ($n = 6$) or only SMV ($n = 1$). Indications for surgery were variceal bleeding ($n = 5$), intractable ascites ($n = 3$), and thrombosed portacaval shunt ($n = 4$). Surgery included: mesocaval shunt ($n = 3$), portacaval shunt with thrombectomy ($n = 3$), splenorenal shunt ($n = 2$), splenic artery ligation ($n = 1$), oesophageal transection ($n = 1$), Leveen shunt ($n = 2$); (b) seven (26 per cent) patients had chronic pancreatitis with thrombosis of PV ($n = 2$), SMV ($n = 3$), or SV ($n = 2$). In two cases, peroperative ileoportography permitted diagnosis of obstruction of SMV without thrombosis, and duodenopancreatectomy was performed; in two cases, SV thrombosis was associated

with variceal bleeding, and left splenopancreatectomy was performed; in two cases, atypical biliary diversion was performed because of portal cavernoma, one cholecystojejunostomy and one hepaticojejunostomy on duct III; in one case, mesocaval shunt was done before duodenopancreatectomy; (c) five (18 per cent) patients had pancreatic cancer and palliative surgical treatment was carried out in all cases; (d) one patient had SV and PV thrombosis with acute pancreatitis, and splenopancreatectomy was done for pancreatic fistula; (e) one patient presented with choledochal cyst and portal cavernoma; splenorenal shunt was performed 18 months before choledochal cyst resection; (f) one patient with a myeloproliferative disorder and portal cavernoma due to PV thrombosis presented with acute cholecystitis; cholecystectomy without cystic duct dissection was performed.

In conclusion, PT associated with cirrhosis was symptomatic in all of our surgical patients. Without cirrhosis, PT was frequently asymptomatic but it modified surgical management in all cases.

Outcome of ascites in bleeding cirrhotic patients treated with portacaval anastomosis or sclerotherapy

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The purpose of this study was to assess the outcome of ascites in 31 bleeding cirrhotic patients included in a randomized controlled trial comparing elective portacaval anastomosis with sclerotherapy.

All patients were classified as Child's grade B; 14 were treated with portacaval anastomosis and 17 with sclerotherapy. The groups were comparable for age, sex, aetiology of cirrhosis, hepatic and renal function and diuretic requirements before randomization.

After treatment, diuretic requirements decreased in the portacaval group (frusemide 34(7) to 2.8(2) mg day⁻¹ ($P < 0.001$); spironolactone 125(11) to 19(8) mg day⁻¹ ($P = 0.0001$)). No change occurred in the sclerotherapy group. During the follow-up period 11 patients (79 per cent) treated with portacaval shunt were free of ascites despite not receiving diuretic treatment, while this situation occurred in only two patients (12 per cent) in the sclerotherapy group ($P = 0.0002$). No further variceal bleeding occurred in the portacaval group while further bleeding occurred in seven (41 per cent) cases in the sclerotherapy group ($P = 0.001$). Hepatic encephalopathy appeared more often after portacaval shunt than after sclerotherapy (seven versus two patients). One patient (7 per cent) from the portacaval group developed chronic encephalopathy. One-year survival rate was higher in the portacaval group (85 per cent) than after sclerotherapy (68 per cent) (P not significant).

We conclude that, in addition to being an effective treatment for variceal bleeding with a low rate of chronic hepatic encephalopathy, portacaval shunt is useful in preventing ascites accumulation in patients with cirrhosis.

Surgical treatment of acute Budd–Chiari syndrome: long-term results

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The long-term prognosis of acute Budd–Chiari syndrome (ABCS) treated surgically is not known. The objective of this study was to report long-term results in ten patients.

From 1976 to 1981, ten patients (seven women and three men, of mean age 30 (range 17–62) years) have undergone operation for ABCS, confirmed by biopsies after the first attack in nine cases and after the second attack in the last patient. A portacaval shunt was performed in four patients to treat isolated obstruction of hepatic veins. Six patients had an obstruction of the vena cava by the diaphragm or by hypoplasia; extracorporeal circulation was used in five patients to allow resection of the membrane (two), dilatation (two), and caval angioplasty (one). Thrombectomy of the cava was performed in four of these patients. The last patient had a dilatation via the jugular vein.

There was no postoperative mortality and the ascites disappeared in all cases. One patient died at 6 months from general metastasis of a kidney cancer. Two patients were lost to follow-up at 6 and 9 months

when they were asymptomatic. The remaining seven patients have been followed for between 4 and 15 years. During this period all the patients had a normal lifestyle without acute attacks or ascites. Five patients had a normal angiogram. One patient died 9 years after operation from a phaeochromocytoma. Two patients have had a myeloproliferative syndrome and disseminated lupus 7 and 9 years after the operation. The remaining four patients are in good health with normal hepatic function.

The surgical treatment of ABCS is effective in alleviating ascites and portal hypertension. Treatment prevents further acute attacks and probably the development of cirrhosis. It allows a normal life-style, but surveillance is necessary to search for general disease, which developed later in 20 per cent of the patients in this short series.

Tumour cell injection in the caecal wall: an experimental model for metastases

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In the rodent model a rhabdomyosarcoma line (RMS S4-MH) metastasizes to the lymph system, lungs and liver after subcutaneous (SC) inoculation. This pattern of spread has been compared to that following intrasplenic (IS) and intracaecal (IC) injection.

After IC injection, tumour was obtained in 80 per cent of cases and survival was similar to that after SC injection. Orderly lymphatic spread of tumour was observed, while liver metastases were rare. There was rapid growth of the primary tumour after IS injection, and liver metastases always developed. Pulmonary metastases were rare after IC (none of five) or IS (two of five) injection.

The intracaecal route of infection has also been tested using an adenocarcinoma line. Local tumour, without peritoneal dissemination, was obtained in 48 per cent of rats. Lymph node metastases were observed in 80 per cent of these animals, while liver metastases developed in only one animal.

In conclusion, the intracaecal route of tumour inoculation allows a comparison of metastatic spread to the lymph system and to the liver in different cell lines. This model may be of use to test adjuvant therapies and in immunoscintigraphy.

Simultaneous devascularization, oesophageal transection and splenorenal anastomosis as a treatment of portal hypertension

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The most dramatic complication of portacaval hypertension is bleeding from oesophageal varices. Surgical treatment can control this. In our surgical department in 1986–1991, 32 patients with portal hypertension caused by prehepatic or intrahepatic block underwent operation. Before operation, all patients reported one or more episodes of bleeding from oesophageal varices. Three of them were Child's grade C, 22 grade B and seven grade A. Until 1988, in treatment of portacaval hypertension, various vascular operations were performed (Drapanas, Blakemore, Warren, Marion, Linton), and a variety of non-shunt operations. In the beginning, in the present series, transection and oesophagogastric anastomosis was made by a traditional method. For 3 years, transection with an ILS-25 appliance complemented by splenorenal anastomosis by the Blake-more method has enabled both kinds of operation to be performed simultaneously. Combination of both operative techniques leads to the reduction of portacaval hypertension, and also prevents rebleeding from oesophageal varices. In 14 cases, simultaneous operations were performed. In this group, three patients died before the 14th day after operation. In 11 cases under observation from 3 to 28 months, no increase in the diameter of the portal or splenic vein was noted on ultrasonographic examination. Gastroscopy in two cases showed first-degree oesophageal varices, and in nine variceal changes have completely resolved. Postoperative biochemistry (albumin, bilirubin, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, γ -glutamyl transpeptidase, prothrombin time and prothrombin level) showed moderate impairment of hepatic function. We are of the opinion that continuous clinical analysis of patients undergoing operation in our department by the simultaneous method or in other clinics by different methods will demonstrate the value of the method we have chosen.

Resection of hepatocellular carcinoma associated with liver disease

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From 1972 to 1989, 43 patients (42 men, one woman) had resection of hepatocellular carcinoma associated with a diseased liver. In 80 per cent of the patients the primary aetiological factor was alcohol. Thirty-two patients had a partial resection of the liver (median age 61 years) and 11 patients had a total hepatectomy with liver transplantation (median age 51 years). The 30-day operative mortality was two patients after partial hepatectomy and four patients after total hepatectomy. The actuarial survival rate at 5 years was 23 per cent for the whole group. The actuarial 3-year survival rate was 36 per cent for both groups. The *Table* shows factors that significantly influence 5-year survival.

Risk factor studied	5-Year survival rate (%)	P
Child's grade A	27	<0.05
Child's grade B	19	
Tumour >3 cm	18	<0.05
Tumour <3 cm	35	
Encapsulated tumour	48	<0.05
Non-encapsulated tumour	21	
α -Fetoprotein <500 ng ml ⁻¹	31	<0.05
α -Fetoprotein >500 ng ml ⁻¹	10	

It is concluded that partial liver resections for hepatocellular cancer in the diseased liver can be undertaken with an acceptably low mortality rate.

Ischaemia and reperfusion liver injury: influence of duration of ischaemia on viability

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Ischaemia and subsequent reperfusion cause functional and structural cellular damage. The purpose of this study was to assess the significance of the length of ischaemic time in ischaemia/reperfusion injury in a model of partial hepatic ischaemia. Male Wistar rats (250–300 g) were used. A loop was placed around the vessels into the left and median lobes, which were temporarily occluded. The periods of ischaemia were 0 (n = 8), 15 (n = 5), 30 (n = 5), 60 (n = 5) and 120 (n = 5) min. Blood samples were obtained 15 min after reperfusion. Serum alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase levels were determined. Plasma malondialdehyde was measured by the thiobarbituric acid method. Twenty-four hours after reperfusion, all the surviving rats were killed and exsanguinated, and livers were submitted to histological study.

	Ischaemia (min)				
	0	15	30	60	120
Aspartate aminotransferase (units/l)	120(8)	596(16)	1506(24)	3204(54)	3533(338)
Alanine aminotransferase (units/l)	506(10)	2529(238)	4016(116)	8081(98)	9984(272)
Malondialdehyde (10 ⁻² nmol/l)	25.6(1.3)	40.8(0.7)	70.6(1.0)	154.7(8.1)	299.9(4.7)
Mortality rate at 24 h (per cent)	0	0	0	10	100

Values are mean(s.d.) after 15 min reperfusion

Light microscopy 24 h after reperfusion did not show significant changes in the 15- and 30-min groups, but scattered necrosis and haemorrhage were evident in the livers that suffered ischaemia for 60 min.

We conclude that the duration of ischaemia is a critical factor affecting the reversibility of cellular injury after reperfusion. The elevated peroxidation indices may indicate the presence of chemically active free radical oxygen species.

Mechanisms of lymphocyte adherence in the reperfused rat liver

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There is a relationship between preservation injury of liver allograft and rejection. An important mechanism of rejection may be lymphocyte adherence on reperfusion of liver grafts since we previously showed that the degree of lymphocyte adherence in sinusoids is strongly related to the length of cold ischaemia¹.

This study was designed to determine whether (1) reactive oxygen intermediates (ROI), (2) leukotriene B₄ (LTB₄), (3) Kupffer cell (KC) products, (4) mechanical obstruction, or (5) cell surface proteins are responsible for lymphocyte adherence. Rat livers were stored at 1°C in University of Wisconsin solution for 45 min or 30 h and then reperfused for 90 min at 37°C in the IPRL. Isogenic rat lymphocytes, prepared on a Ficoll-Paque gradient, were added to the bloodless perfusate. The role of ROI was investigated by adding allopurinol, Trolox-Vit C, or superoxide dismutase-catalase to the perfusate. LTB₄ was examined by a lipo-oxygenase inhibitor (NDGA). KC blockade was produced by intravenous gadolinium (Gd). The importance of protein receptors was assessed by trypsinization of lymphocytes and by adding arabinogalactan (a galactose glycoconjugate) to the perfusate.

In livers preserved for 45 min, lymphocytes decreased 39.8–46.8 per cent during reperfusion. In livers preserved for 30 h, the reduction was significantly greater (76.4–80.8 per cent). In livers preserved for 45 min, reperfused with any of the three ROI protectants, lymphocyte adherence was significantly reduced to 8.3–36.3 per cent. In Gd-pretreated rats, lymphocyte decrease in livers preserved for 45 min was also significantly reduced (range: 20.4–33.8 per cent). In contrast, ROI protectants and Gd did not affect the results in livers preserved for 30 h. Portal flow upon reperfusion was similar in both groups, suggesting absence of mechanical obstruction. In support of this, livers reperfused with 35 000 red cells mm⁻³ had no change in the number of circulating red cells. The use of trypsin or arabinogalactan prevented lymphocyte adherence in 30-h livers but not in 45-min livers. NDGA had no effect in either group of livers.

The study shows that there are two distinct mechanisms of adhesion, one operative after short periods of preservation (ROI and KC) and another after longer periods (cell surface proteins).

1. Clavien P-A, Morgan GR, Sanabria JR *et al.* Effect of cold preservation on lymphocytic adherence in the perfused rat liver. *Transplantation* 1991; 52: 412–17.

Renal impairment following intravenous injection of ethanolamine oleate

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It is becoming clear that injection sclerotherapy of oesophageal varices can result in systemic complications. The aim of this study was to investigate the relationship between platelet aggregation and renal blood flow (RBF) and function (RF) after administration of ethanolamine oleate (EO) to rats and in patients after injection sclerotherapy. Organ blood flow (microsphere technique) was measured 1 h and 24 h after intravenous administration of EO (0.05 ml 100 g⁻¹) to portal hypertensive rats. RBF and RF were determined by plasma clearance of Mag3, a renal tubular agent. Mag3 renography and platelet counts were also measured in cirrhotic patients before and after injection sclerotherapy. In rats, intravenous EO resulted in a rapid fall in the mean (s.e.m.) platelet count (822(36) × 10⁹ litre⁻¹ to 668(50) × 10⁹ litre⁻¹/h) which was associated with microscopic or macroscopic haematuria. RBF was unchanged after 1 h or 24 h. RF was significantly impaired 24 h after EO administration (0.65(0.08) ml min⁻¹ 100 g⁻¹ compared with controls (1.67 (0.19) ml min⁻¹ 100 g⁻¹/h). Similar but less dramatic changes were observed in patients after sclerotherapy. Haematuria was present in three of nine, with some evidence of renal impairment. However, the very low initial platelet counts in these patients is a confounding factor. These observations suggest that hepatic and renal necrosis and impairment of RF after administration of EO are not associated with alterations in RBF but may be secondary to platelet microembolization.

Tumour extension (T parameter) and grading of anaplasia (G parameter) in TGS system for staging supratentorial gliomas

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The classification in stages of evolution represents an objective way to describe neoplastic disease through the different steps of its natural history. The main variables which influence tumour evolution are its anatomical extension (T parameter) and its biopathological features (G parameter). The subdivision in groups for staging was carried out on the basis of the TGS system. T factor was divided into three categories according to the maximum diameter, as shown by computed tomography and/or magnetic resonance imaging: T₁ (<3 cm), T₂ (3–5 cm) and T₃ (>5 cm). Tumour grading was evaluated according to World Health Organization classification (G₁–G₄).

To evaluate the influence of these variables on tumour evolution and their suitability as a staging classification, two different series of supratentorial gliomas were analysed. The first included 137 cerebral tumours. All of them underwent a stereotactic biopsy. The histological diagnosis was astrocytoma in 67 cases, oligodendroglioma in 27 and glioblastoma in 43. The second series concerned 60 patients (23 anaplastic astrocytoma and 37 glioblastomas), who underwent surgical resection by craniotomy. After operation, all patients received conventional radiotherapy, up to a total tumour dose of 60 Gy. Grading showed a high positive correlation with survival for all groups considered. For example, in the biopsy series (group T₃), the 1-year survival rate was 85.7 per cent in G₂, while it dropped to zero in G₃. The category G₂/G₃ when compared with G₂ and G₃ respectively showed a closer affinity to the latter. Regarding factor T, in group G₄ of the surgical series, the 1-year survival rate of T₂ was 45 per cent, while in T₃ the survival probability was zero.

These data seem to confirm the prognostic relevance of T and G parameters. Furthermore, multivariate analysis showed a 'hierarchy' in their relative significance: the G factor was the most important independent variable followed by T. The endpoint of this research will be to define different categories suitable for a staging classification in neuro-oncology.

Epileptic seizures and arteriovenous malformations of the brain

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In a 3-year period (1980–1982), 36 patients with arteriovenous malformations were treated. The most common presenting symptoms were intracranial bleeding in 14 (39 per cent), epileptic fits in ten (28 per cent) and headache in seven (19 per cent). In all, 16 patients suffered from fits, generalized in five and focal in 11.

Two patients with basal ganglion lesions had non-operative treatment, while the remainder were treated surgically. The most common site for the lesion was parietal (ten patients), followed by ten focal lesions (in seven patients) and frontal lesions (six patients). These three sites accounted for most of the patients with fits, with the parietal region being proportionately the most frequent site.

After operation 18 patients suffered from epileptic fits, eight generalized and ten focal. Of these, ten had suffered from fits before operation. These included all those who had had generalized fits and nearly half of those with focal fits.

These results demonstrate that removal of the lesion does not necessarily cure the epilepsy. Electrocortigraphy should be included in the surgical management of these patients.

Intracranial compression syndrome during treatment of multiple trauma

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Head injury, as the dominant type of injury in multiple trauma, is the usual cause of more severe sequelae, in particular the intracranial compression syndrome, which requires neurosurgical intervention.

From 1 January 1988 to 1 July 1991, 188 patients with multiple injuries and predominant craniocerebral injury were treated in the Institute for Emergency Medicine of the University Clinical Centre, Belgrade. Ninety-two patients underwent neurosurgical operations and form the subject of the present paper. Forty-one patients underwent operation for subdural haematoma, 22 for epidural haematoma and 25 patients for depressed skull fracture.

The mortality rate was higher in patients with multiple injuries in addition to severe head injury and the intracranial compression syndrome than in those with craniocerebral injuries alone.

The mortality rate of multiply injured patients with acute subdural haematoma was 89 per cent. In acute subdural haematoma and severe chest injury the rate increased greatly: only one young patient survived. The mortality rate of patients with extradural haematoma was 67 per cent whereas that for patients with closed depressed skull fracture was 54 per cent.

In conclusion, intracranial compression syndrome is associated with poor outcome in multiply injured patients.

Apart from the type of intracranial compression syndrome involved, the survival rate was also influenced by the level of consciousness at admission, as well as the neurological findings and the age of the patient.

Hormonal changes in the development of brain death

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Circulatory collapse in organ donors requires administration of catecholamines at high dosages with adverse effects on the transplant organs. Hormones have a direct influence on organ perfusion and metabolism as well as on susceptibility to the catecholamines administered. The object of this prospective investigation was to evaluate hormonal alteration during development of brain stem death.

Forty patients with severe head injury ($n = 21$) and intracerebral haemorrhage ($n = 19$) were included. Thyroid-stimulating hormone (TSH), tri-iodothyronine (T₃), tetraiodothyronine (T₄), thyroxine-binding index, thyroxine-binding globulin, human growth hormone, cortisol adrenocorticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone and aldosterone were monitored at the following times: (1) on clinical investigation; (2) on Doppler sonography; (3) at digital subtraction angiography; and (4) at the time of organ donation.

All patients developed a marked reduction in thyroid hormone levels, especially of T₃. TSH remained subnormal, as did ACTH, cortisol and prolactin. FSH and LH were in the normal range. Correlation analysis revealed continual negative dependencies between thyroid hormone and dopamine levels during the course of brain death. The pituitary-hypothalamic axis for TSH and T₃/T₄ was impaired. We conclude that T₃ substitution could be a helpful tool in the maintenance of organ donor circulation and in diminishing the adverse effects of catecholamine administration by lowering dopamine requirement.

Gait analysis as an aid to decision making in cerebral palsy

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A prospective study was made of the role of gait analysis using the CODA 3 motion analyser as an aid to decision making in the management of 180 patients with cerebral palsy over a 2-year period. CODA 3 is a light-scanning system based on three rotating mirrors which emit beams of light. These beams are reflected from coloured pyramidal markers which are placed on the surface of the body being analysed and the reflected light pulses are optoelectronically identified providing three-dimensional data for each marker. This yields immediate gait analysis data, in a non-invasive and 'patient friendly' fashion, which is easily and immediately interpretable. Patients were assessed clinically before intervention. The management decision based on clinical assessment was recorded. Gait analysis was then performed. Certain features of precise gait analysis which prevent inappropriate or unnecessary surgery were identified. The management decisions were based on the gait analysis data. The

patients were recommended physiotherapy, orthosis or surgery. The efficiency of the management decisions, based on CODA 3 data, was assessed using gait analysis after intervention.

We found the CODA 3 system to be safe, effective and an essential tool in patient evaluation and treatment selection.

Evaluation of intraoperative real-time ultrasonography in microsurgery of deep-seated brain tumours

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The development of intraoperative real-time ultrasonography during intracranial procedures is useful for the neurosurgeon. Ultrasonography remains the only technique providing continuous imaging information to the surgeon during a procedure.

The principal use is the localization of lesions where the overlying cortical surface appears normal. Before the introduction of stereotactically guided resections or ultrasonographically guided procedures, the surgical management of deep-seated brain tumours was controversial. The main problem to be faced during the surgical approach is correct localization of the lesion while sparing healthy brain tissue. Between March 1988 and December 1991, 55 consecutive deep-seated tumours were operated on: 23 metastases, 11 glioblastomas, four fibrillary astrocytomas, seven anaplastic astrocytomas, four oligodendrogliomas, two pilocytic astrocytomas, two ependymomas, one cavernoma and one lymphoma. The lesions ranged in size from 1 to 6 cm in maximum diameter; their location was hemispheric in 46, thalamic in four, intraventricular in three and cerebellar in two.

Surgical resection, usually performed by the microsurgical integral approach, allowed a gross total removal (tumorectomy) in 28 patients (51 per cent), a subtotal removal (residual disease <10 per cent) in 17 (31 per cent), and a partial removal in ten (18 per cent). In seven patients (13 per cent) we observed the temporary appearance, or extension, of neurological deficits. Two patients died within 1 month of surgery. These data confirm that intraoperative ultrasonography makes an operation safer for the patient and generally shortens the duration of operation.

Spinal cord stimulation in failed back surgery syndrome

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This study reviews experience with spinal cord stimulation in treating the failed back surgery syndrome. Patients were selected after clinical assessment, neuroradiological investigations and electromyography if they had excellent pain relief during 1 week of trial stimulation and no major psychiatric or psychological pathology. Seventy-eight patients underwent trial stimulation. Of these, 14 (18 per cent) failed to obtain excellent pain relief during 1 week of stimulation and their electrodes were removed. The remaining 64 underwent a definitive implant and were followed for a mean of 4 (range 1–8) years. A group of 35 patients (55 per cent) continued to experience at least 50 per cent pain relief at the latest follow-up. In all, 58 patients (91 per cent) were able to reduce their medication and 39 (61 per cent) reported a change in lifestyle, in that their ability to perform daily activities had improved significantly at the latest follow-up.

Extent of surgical resection (S parameter) in the TGS system for staging supratentorial malignant gliomas

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Neurosurgical dogma states that the radical surgical removal of brain tumours, when feasible, is crucial in improving patient survival.

Unlike the tumour node metastasis (TNM) system, we have considered the following parameters for staging of malignant hemispheric gliomas: T (T₁–T₃), tumour extension; G (G₁–G_{IV}), grading of anaplasia; and, finally, S (S₁–S₃), degree of surgical resection. Tumour removal, usually performed with a microsurgical approach, was evaluated as follows: S₁, tumorectomy (up to the tumour borders), 'wide tumorectomy' (>2 cm from the tumour

borders) or lobectomy including the tumour; S₂, residual disease <10 per cent; S₃, partial removal. Such a subdivision is arbitrary, but can nevertheless be of practical use in the assessment and comparison of data. To evaluate the S parameter, postoperative computed tomography (CT) scans and/or magnetic resonance imaging were always performed within 3 weeks of surgery and before the beginning of radiotherapy. Sixty patients with malignant gliomas were included in the study. All underwent surgical resection by craniotomy. Survival time and actuarial survival curves (Berkson and Gage or Kaplan–Meier actuarial methods; Lee–Desu statistical analysis) were evaluated for the different groups; furthermore the log rank test, the Cox proportional hazards model and Pearson correlation matrix analysis were employed to assess the relative prognostic value of S parameters. The 1-year overall survival probability was 68 per cent in the S₁ group, 40 per cent in the S₂ group and 11 per cent in the S₃ group. The 1-year survival probability in malignant astrocytoma (G_{III}) was 100 per cent in the S₁ group, 66 per cent in the S₂ group and 43 per cent in the S₃ group. Analysis of the glioblastoma series gave a 1-year survival probability of 46 per cent in the S₁ group, 17 per cent in the S₂ group, while it dropped to zero in the S₃ group.

These data seem to confirm the prognostic relevance of the S parameter and suggest that the TGS system has value in neuro-oncology.

Sacral meningeal cyst surgery in the treatment of chronic perineal pain

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Based on a series of 17 patients in whom urological, gynaecological and anorectal pathology was excluded, we compared magnetic resonance imaging (MRI) with computed tomographic myelography (CTM) in the investigation of chronic perineal pain. After a clinical neurological examination, patients underwent radiodiagnostic imaging using both techniques. Thirteen patients (76 per cent) had one or more sacral meningeal cysts (MC) on MRI, whereas CTM of the lumbar and sacral region revealed seven patients (41 per cent) with sacral MC. Sacral MC may be the cause of chronic perineal pain in many instances and MRI appears to be superior to CTM in demonstrating them. Operations were carried out on ten patients with sacral MC with moderate to excellent results 6 months after operation. Early postoperative results are encouraging, but further follow-up and larger series are required.

Comparison between vein graft conduits and plain suturing in peripheral nerve reconstruction in rabbits

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Positive results of tubularization as a way of reconstruction for peripheral nerves in animals have been seen by many investigators. Clinically, tubularization by means of a vein graft conduit is accepted as a reliable technique, but histological results are not known and functional analysis is limited. Our aim was to study the effect of vein graft conduits in peripheral nerve reconstruction.

In 20 rabbits, 30 saphenous nerves were divided. In the first series (n = 10) an autologous vein graft conduit was placed around a primarily epineurally sutured nerve. In the second series (n = 10) an autologous vein graft conduit was fixed epineurally over a nerve gap of 3 mm and the free nerve endings; division of the saphenous nerve was performed contralaterally and this was simply epineurally sutured to serve as the control series. Healing was studied for a period varying from 2 weeks up to 3 months.

Histological comparison between the techniques with the vein graft conduits on one side and the untubularized nerve suture on the other side did not show a favourable effect in either vein graft procedure. On the contrary, extensive fibrous tissue was formed in the vein graft anastomoses, impeding passage of the regenerating axons through the gap or the approximated anastomosis. The untubularized procedure showed a more ordered pattern of nerve tissue.

Our experiments show that covering an anastomosis or gap of the saphenous nerve in rabbits with a vein graft conduit did not enhance the healing in comparison to the classical end-to-end anastomosis. The graft procedure evoked extensive fibrous tissue, hampering regeneration of axons.

Needle catheter jejunostomy: a safe method to secure nutrition after extensive upper gastrointestinal surgery

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The effectiveness and complications in postoperative enteral nutrition using a needle catheter jejunostomy (NCJ) were evaluated in a retrospective trial. After extensive upper gastrointestinal surgery, an NCJ was placed in 238 patients to start enteral nutrition on the third day after surgery. In all patients the energy requirements were fulfilled on the sixth postoperative day by total enteral nutrition. The mean feeding period was 22.6 days in 191 patients with no postoperative complications, 35 days in 17 patients with insufficient anastomosis, and 90 days in 30 patients who were fed via the NCJ even after discharge in a home-feeding programme. There was one dislocation of the catheter (0.4 per cent). Accidental removal of the NCJ by patients was observed in ten cases (4 per cent). The main complications during enteral nutrition were diarrhoea, distension, nausea or abdominal bloating in 53 patients (22.3 per cent). This required cessation of feeding in 30 patients (12.6 per cent). After a feeding period of 13 days, constant body-weight and increasing serum albumin concentrations were found in all patients. Because of the low complication rate, enteral feeding by NCJ is not only an alternative in patients undergoing upper gastrointestinal surgery, but should be preferred because of the possibility of long-term feeding in patients who develop postoperative complications. Even after discharge, the patient can easily be fed with the comfortable NCJ in home-feeding programmes.

Prospective clinical trial of total parenteral nutrition in digestive surgery

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We have compared four different types of total parenteral nutrition (TPN) in the postoperative treatment of patients undergoing major digestive procedures. Fifty-six patients meeting inclusion criteria were randomly assigned to one of the four different dietary groups (1-4) and were evaluated for 1 week.

Nutritional component	Group			
	1 (n=14)	2 (n=15)	3 (n=14)	4 (n=13)
N (g kg ⁻¹ day ⁻¹)	0.24	0.24	0.24	0.24
BCAA/AA	10.3	10.3	10.3	18.3
CH (g kg ⁻¹ day ⁻¹)	3	3	3	4.2
Lipids (g kg ⁻¹ day ⁻¹)	—	1.3	1.3	1.9
LCT:MCT	—	1:0	1:1	1:0
N:kcal	1:50	1:100	1:100	1:140
kcal kg ⁻¹ day ⁻¹	12	24	24	24

N, nitrogen; BCAA, branched chain amino acids; AA, total amino acids; CH, carbohydrates; LCT, long chain triglycerides; MCT, medium chain triglycerides. Carbohydrates were given as a fructose-glucose-xylitol mixture in proportions of 2:1:1

No statistically significant differences (ANOVA) were found between regimens when nutritional parameters that measure short-term nutritional efficacy (nitrogen balance, serum albumin, prealbumin and transferrin) were studied. However, a positive trend towards the seventh day in these parameters was found in each group (ANOVA). Although no significant differences between groups were found, a more positive trend was observed in the group 4 patients, who received more calories and a BCAA-enriched amino acid solution.

We conclude that in a non-complicated 1-week fast after major surgery, a hypocaloric intravenous diet, such as the one used in the group 1 series, is sufficient to maintain or improve the patient's nutritional status. When complications are suspected or have

occurred, and fasting lasts longer than 1 week, we recommend a normocaloric BCAA-enriched intravenous diet similar to that used in the group 4 patients.

Value of percutaneous endoscopic gastrostomy for the feeding of unconscious patients

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From 1984 to 1990 percutaneous endoscopic gastrostomy was performed in 30 comatose patients. Frenett-Set gastrostomy equipment (Fresenius) was used, with the catheter having one longer arm to enable alimentation directly to the duodenum.

The indications for this procedure were: multiple system failure (five cases), coma after head injury (six), cerebral damage after resuscitation (12), intracranial haemorrhage (five) and brain tumour with coma (two).

There were no complications resulting from the procedure itself. In two patients leakage of the gastrostomy canal developed, but did not require intervention. In six cases the catheter slipped from the duodenum to the stomach; it was corrected on endoscopy. The patients were fed for between 2 and 65 days.

Percutaneous endoscopic gastrostomy is very useful in intestinal feeding of unconscious patients; it does not require general anaesthesia; it is easy to do; and the results are quite satisfactory.

Lipid-based total parenteral nutrition in the complex treatment of severe acute pancreatitis

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Patients with severe acute pancreatitis (SAP) often require parenteral nutrition (TPN). Because the administration of lipids in patients with SAP is controversial, a series of such patients was studied in order to evaluate the safety and efficacy of lipid-based TPN.

Lipid-associated TPN was given to 21 patients with SAP (group A). Another eight patients received standard glucose-based TPN (group B). The control group consisted of 40 patients treated traditionally without TPN. In both groups the severity of the disease was assessed according to a modified Ranson scale. The safety and efficacy of lipid-based TPN was assessed by comparing the clinical course, frequency of complications and results of treatment. Lipid profiles were determined in all parenterally fed patients.

Group	No. of patients	Serum triglycerides (mmol l ⁻¹)			
		Before TPN	During TPN	After TPN	Mean TPN duration (days)
A	21	1.43(0.6)	1.51(0.8)	1.55(0.6)	27.7(5)
B	8	1.84(0.9)	1.73(0.6)	2.54(0.9)	15.3(6)

Values are mean(s.e.m.). Normal triglyceride value: 0.79-1.73 mmol l⁻¹

No exacerbations of pancreatitis were attributable to lipid-based TPN. Nutritional status was improved in all patients receiving TPN, while most of the traditionally treated patients developed severe nutritional depletion. The plasma total protein and albumin levels were significantly higher in patients receiving TPN than in patients treated traditionally in whom profound nutritional depletion developed during the course of the disease. TPN had no significant influence on the development of complications which developed in 52 per cent of patients from the first, and in 63 per cent of patients from the second group. Surgery was necessary in 58 per cent and in 42 per cent of patients respectively. Mortality rates were 10 per cent in the first and 28 per cent in the second group of patients.

We conclude that the lipid-based system of TPN is safe, effective and well tolerated in patients with SAP.

Effects of long-chain lipids on gastric emptying in rats subjected to total parenteral nutrition

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In the field of parenteral nutrition (PN), few substances have met with as much controversy as lipids. Although these have always been regarded as essential to any balanced diet, and lipids are in fact extensively used in PN, their effects on gastrointestinal motility are poorly understood. This aspect is of importance, as gastrointestinal function may be altered as a result of either PN administration or the nutrients utilized.

In the present paper we study the effects of long-chain lipids on gastric emptying in conscious rats subjected to PN. Wistar rats (250–280 g) of either sex were used. After intramuscular ketamine anaesthesia (200 mg kg⁻¹), cannulae were positioned surgically within the left jugular vein and fitted to the perfusion system via a swivel attached to the rat by a protective jacket. The animals were housed in metabolic cages, with a 48-h recovery period before PN. The rats were infused for 5 days with a solution providing 218 kcal kg⁻¹ day⁻¹ and 7.6 g of amino acids kg⁻¹ day⁻¹. The energy content corresponded to different proportions of glucose and lipids: diet A (100 per cent glucose); diet B (5 per cent lipids); and diet C (40 per cent lipids). Infusion rate was fixed at 2 ml h⁻¹. Gastric emptying was determined by analysis of phenol red (0.5 per cent) in gastric juice 20 min after oral administration, determined by spectroscopy (560 nm). There were 14 animals per group, and statistical analysis of the results was performed by applying Student's *t* test.

Gastric emptying in the controls (diet A) was 54.9(6.4) per cent, similar to the results reported in the literature. The incorporation of 5 per cent lipids (diet B) failed to alter gastric emptying significantly (57.9(5.3) per cent) with respect to the controls (*P* > 0.05). On the other hand, when lipid energy contribution was 40 per cent, gastric emptying increased significantly (78.8(3.2) per cent; *P* < 0.05).

The accelerating effect of total PN with long-chain lipids contrasts with the established inhibiting effect of orally administered lipids on gastrointestinal motility. This effect may have clinical applications in cases of functional gastric stasis.

Totally implantable device versus external catheter for intravenous therapy in patients with neoplastic disease

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The purpose of the study was to assess the efficacy of totally implantable devices and external catheters in intravenous therapy of adult patients with non-haematological neoplastic disease.

Between January 1989 and December 1990, 138 external catheters were placed percutaneously, 132 of them through the

subclavian vein. There were also eight failed attempts. Between May 1989 and August 1991, 85 implantable devices were placed in 81 patients, 61 of them through cut-down of the external jugular vein.

Early complications after placement of external catheters (20 of 146) included six cases of pneumothorax. Among the late complications, involuntary removal of the catheter (21 patients) and occlusion (12) were the most important. The average number of days per catheter placed was 56 (range 0–256).

The implantable devices had an early complication rate of 5 per cent (four of 85), and 14 per cent late complications, mostly infections, leading to withdrawal (12 of 85). The average number of days per device withdrawn was 258 (range 15–770). It is concluded that maximum asepsis is crucial to avoid infective complications.

In this study external catheters were less effective than implantable devices (34 per cent of withdrawn catheters versus 14 per cent of withdrawn devices for late complications). We think that implantable devices are the system of choice for antineoplastic long-term chemotherapy, because of their lower complication rate, and their higher durability and comfort for the patient.

Value of preoperative clinical and biological study of haemostasis: a prospective study in 2918 patients

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During a 4-year period, 2918 patients were included in a multicentre prospective study to compare the diagnostic value of oriented clinical and biological examinations in predicting morbidity and/or mortality due to haemorrhage.

In all, 1426 men and 1492 women with a mean age of 50.5 (range 2–99) years undergoing elective or emergency surgery were included. Patients undergoing operations with local anaesthesia, orthopaedic operations, stripping of varicose veins, haematoma, as well as patients with preoperative anticoagulation, were excluded. Clinical examination was considered abnormal when there was a history or signs of haemorrhagic accident or disease, or treatment with drugs acting on haemostasis. Laboratory findings considered as abnormal included: Quick's time < 70 per cent; activated cephalin time > 1.2 × control; platelets < 120 × 10⁹ litre⁻¹; and bleeding time > 1 × control value.

Four groups were defined: (1) no clinical and/or biological abnormalities, 1740 patients; (2) isolated laboratory abnormalities, 326 patients; (3) isolated clinical abnormalities, 692 patients; (4) clinical and laboratory abnormalities, 160 patients. There were four postoperative deaths from haemorrhage, with no significant difference found between the four groups. In addition, the specific postoperative complications (haematomas, ecchymoses, reoperations for bleeding) were not found to be significantly different. The perioperative strategy was modified only in the presence of clinically abnormal results (groups 3 and 4), with no modification in group 2.

These results support the policy of requesting laboratory investigations only in patients with clinical abnormalities (852 of 2918, or about 30 per cent of the studied population).

Manometric follow-up after resection of Zenker's diverticulum

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The long-term results after resection of Zenker's diverticulum with and without myotomy were compared. The function of the upper oesophageal sphincter was evaluated by manometry.

Fifteen patients had undergone surgery for Zenker's diverticulum. We were able to follow up six of them after a mean of 4 years (range 5 months to 10.5 years). Preoperative manometry on one patient revealed markedly impaired coordination between pharyngeal contraction and relaxation of the upper sphincter. After resection of the diverticulum and myotomy of the upper sphincter this was not observed in any of the patients. Myotomy was also followed by significant lowering of resting pressure in the upper sphincter to mean levels of 18 mmHg (normally 90–100 mmHg). By contrast, one patient who did not undergo intraoperative myotomy had only a moderate reduction of resting pressure to 30–45 mmHg and a normal maximum contraction pressure of 100 mmHg. This patient developed a relapse.

Our manometric evidence underscores the importance of intraoperative myotomy as an adjunctive procedure in diverticulum resection. By helping to reduce distal resistance it also results in a lower rate of relapse.

Leiomyoma of the oesophagus

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Leiomyoma is an infrequent benign tumour of the oesophagus and is generally considered to be a harmless condition. Between 1971 and 1989, 24 patients with leiomyoma of the oesophagus have been treated. In eight patients (33 per cent) the leiomyoma was complicated by documented gastro-oesophageal reflux and oesophagitis. Treatment was always surgical and consisted of enucleation in 21 patients which in six was combined with a Belsey mark IV antireflux procedure. In three patients, enucleation was judged impossible and resection followed by coloplasty was performed. There was one postoperative death which occurred after resection and coloplasty. Long-term follow-up showed no recurrences.

A case is reported of a patient who initially had all features of a leiomyoma at the level of the gastro-oesophageal junction. Pathological examination revealed a low grade malignant leiomyosarcoma for which subsequently a resection and coloplasty was performed.

In conclusion, in this series, leiomyoma of the oesophagus was complicated by reflux oesophagitis in 33 per cent of cases. Oesophagitis may result in difficulty in enucleating the tumour; more complex resectional surgery and subsequent restoration of continuity may be required.

Although there is currently a tendency to monitor leiomyomas by endoscopic ultrasonography especially in asymptomatic patients, the possibility of malignant degeneration must be kept in mind. This consideration, together with the recent development of minimally invasive surgical techniques, favours surgical removal. In this respect an enucleation of a voluminous quasi-circular leiomyoma was frequently successfully performed through a thoracoscopic approach.

Surgical treatment of perforation of the distal part of the thoracic oesophagus with unipolar exclusion using a stapling device

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The prognosis of perforation of the thoracic oesophagus, whether spontaneous or traumatic in origin, is generally serious. In patients presenting late, there is a high risk of early suture breakdown. Oesophageal exclusion associated with suture of the perforation and with mediastinal and pleural drainage improves the prognosis.

This study presents 11 patients treated by this procedure during the past 6 years. There were six men and five women. The mean (range) age was 54.5 (33–76) years. The surgical procedure, in all cases, included a left thoracotomy, suture of the perforation on a T tube and exclusion of the oesophagus under the perforation with a TA55 stapler (US Surgical); absorbable sutures were used in nine cases, non-absorbable in two cases at the beginning of the series. A feeding jejunostomy was performed through a small abdominal approach.

Two deaths (18 per cent) occurred on the 16th and 26th day after operation related to persistent mediastinal sepsis. Oesophagectomy was necessary in one patient at the 70th day for persistent sepsis. In the other cases, the oesophagus could be preserved with spontaneous reopening for the absorbable staples; a gastrotomy for digital reopening was made when absorbable staples were used.

The results of this procedure are promising. We propose its use for the treatment of perforation of the distal thoracic oesophagus presenting late.

Oesophageal scintigraphy: new trends

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Radionuclide oesophageal transit study provides quantitative information of oesophageal emptying. There are, however, discrepancies in results obtained with transit study mainly due to the different techniques employed (liquid, solid or semisolid bolus; single phase or multiphasic ingestion). The purpose of this study was to present a scintigraphic approach overcoming this problem and to compare our standardized transit study technique with oesophageal manometry in detection of motility disorders. Thirteen consecutive patients (nine men and four women, mean age 65 years) with oesophageal motor disorders (Zenker's diverticulum, three; mid-thoracic diverticulum, two; nutcracker oesophagus, three; diffuse oesophageal spasm, two; achalasia, three) underwent both transit study and manometry from June 1990 to June 1991. Transit study was carried out after a 6–8-h fast with single phase ingestion of technetium-99m radiolabelled solid and liquid bolus; patients were studied in the supine position (liquid bolus) and in the upright position (solid bolus). In order to determine control values ten asymptomatic normal volunteers (six men and four women, mean age 26 years) were studied using the parameters described above. Using manometry as the standard, the results of the transit study were as follows: sensitivity for detection of motor dysfunction was 83.3 per cent with solid bolus and 91.6 per cent with liquid; specificity was 81.8 per cent with solid and 72.7 per cent with liquid bolus; predictive value of a positive test was 83.3 per cent with solid and 78.6 per cent with liquid bolus; predictive value of a negative test was 81.8 per cent with solid and 88.8 per cent with liquid bolus.

The liquid bolus test has greater sensitivity, while the solid bolus test has a greater specificity. In conclusion, it is essential that transit studies be standardized in order to obtain comparable results; a solid and liquid single phase technique seems to be the most reliable.

Early extubation and postoperative mortality after oesophageal resection

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Overnight mechanical ventilation has become accepted practice after major surgery but weaning difficulties are frequent and ventilatory support is associated with alveolar trauma. After a policy change in January 1990, early extubation became mandatory in all but the most seriously compromised patients undergoing elective oesophagectomy. Two patient groups were compared: group 1 ($n=36$) underwent oesophagectomy in the year before and group 2 ($n=45$) underwent oesophagectomy in the year after the change in policy.

Both groups were comparable for age, sex and respiratory risk factors.

	Group 1 (n = 36)		Group 2 (n = 45)		P*
No. ventilated overnight	28	(78)	7	(16)	<0.001
No. on prolonged ventilation	10	(28)	2	(4)	<0.005
No. reventilated	7	(19)	0	(0)	<0.002
Mean time on ventilator (days)	4.6		1.1		<0.05
90-Day mortality	6	(17)	2	(4)	n.s.
Mean stay in intensive care unit (days)	9.8		5.9		<0.05

Values in parentheses are percentages. n.s., Not significant; * χ^2 and Mann-Whitney U tests

Early extubation was possible in 84 per cent of patients with no adverse sequelae but with a significant reduction in morbidity. No patient required ventilation and the total time on a ventilator was significantly reduced. These findings support the view that prompt extubation avoids added postoperative risks of pulmonary complications.

Alimentary comfort and social rehabilitation after subtotal oesophageal resection and gastric pull-up

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Responses to a follow-up questionnaire or a personal interview given by 57 patients who had been operated on by a subtotal oesophagectomy and gastric pull-up to the neck are presented. Digestive continuity had been restored using a gastric tube with resection of the lesser curvature in 31 patients (group A) and the entire stomach without resection of the lesser curvature in 26 patients (group B). Median follow-up period was 36 months (group A: 42, group B: 22, $P < 0.005$).

Eighteen patients (32 per cent) led active lives outside the home, 30 (53 per cent) led active lives at home and nine (16 per cent) were inactive. Current body-weight when compared with that which had existed after surgery was unchanged in 14 per cent of the patients (A: 10 per cent, B: 19 per cent), increased in 75 per cent (A: 77 per cent, B: 73 per cent) and decreased in 11 per cent (A: 13 per cent, B: 8 per cent). The mean number of main meals per day was three (A: 2.9, B: 3) and the number of snacks between main meals was 1.6 (A: 1.8, B: 1.4).

Mean rating given by patients themselves to their current alimentary comfort in comparison with that which had predated the initial oesophageal symptoms was 7.9 of 10 (A: 7.6/10, B: 8.2/10). Residual symptoms were early fullness during eating in 51 per cent of the patients (A: 71 per cent, B: 27 per cent, $P < 0.001$), sweating after eating in 10 per cent (A: 6 per cent, B: 15 per cent), vomiting on coughing in 10 per cent (A: 10 per cent, B: 11 per cent), cervical heartburn in 5 per cent (A: 0 per cent, B: 11 per cent), and tachycardia after eating in 3 per cent (A: 0 per cent, B: 8 per cent).

Postoperative dysphagia requiring several sessions of endoscopic dilatation was experienced by 16 per cent of the patients (A: 26 per cent, B: 4 per cent, $P = 0.02$). At follow-up, 14 per cent of the patients complained of slight residual dysphagia (A: 16 per cent, B: 11 per cent). More or less disabling diarrhoea was present in 58 per cent of the patients just after surgery, and in 25 per cent in the long term (A: 19 per cent, B: 31 per cent).

The entire stomach appears to be superior to the gastric tube in significantly reducing the incidence of early fullness during eating and the risk of cervical anastomosis stenosis.

Hand-sewn versus stapled oesophagojejunostomy

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A retrospective study comparing hand-sewn and stapled oesophagojejunostomy was undertaken in order to evaluate the difference in postoperative mortality and morbidity rates, anastomotic leakage and the duration of operative time and hospital stay. From January 1982 to December 1991 a total of 236 patients underwent total or

near-total gastrectomy with systematic lymphadenectomy for carcinoma of the oesophagogastric junction. In 117 patients hand-sewn, two-layer interrupted polyglactin end-to-side oesophagojejunostomy was performed and in 119 patients anastomosis was performed with an EEA stapler (US Surgical) in an end-to-side manner.

	Hand-sewn group	Stapler group
No. of patients	117	119
Mean(s.d.) operating time (min)	300(40)	270(40)
Postoperative mortality rate (%)	11.1	4.5
Anastomotic complications (%)		
Leak	7.7	4.5
Bleeding	1.7	0.9
Stricture	0.9	3.6
Other complications (%)	19.7	9.1
No. of surgeons	11	5

The results presented suggest that oesophagojejunal anastomosis with the EEA stapler is more reliable than hand-sewn anastomosis. Mechanical anastomoses are simple, uniform, fast and individual factors are eliminated. Stapled anastomoses seem to reduce postoperative mortality and leakage, and a statistically significant difference between the two groups was reached. The authors conclude that stapled anastomoses have some advantage over hand-sewn techniques.

Non-malignant oesophageal fistula in adults

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In the past decade, eight adult patients were admitted for a non-malignant oesophageal fistula which had developed into adjacent organs: three caustic fistulae of the oesophagus into the left main stem bronchus, one perforation of a mid-third oesophageal diverticula into the mediastinum and peripheral bronchi, one reopening of a type III tracheo-oesophageal fistula which occurred 23 years after neonatal surgical management, one fistula of an abdominal Nissen fundoplication into the oesophagus, one oesophagopleurobronchial fistula which developed 25 years after an intrathoracic Nissen fundoplication and one tracheo-oesophageal fistula which was mycotic in origin. Presenting symptoms were acute pneumonitis in four patients, recurrent mediastinal abscess and pneumonitis in one, coughing fits in one, chronic heartburn in one and an acute bronchospastic crisis in one.

Management of the fistula was medical in one patient and surgical in seven patients: the operation consisted of excision of the fistulous tract, and oesophageal suture and wrapping in two patients, segmental oesophagectomy with end-to-end oesophago-oesophagostomy in one patient, a cervical oesophagostomy followed by colon interposition in a second operating session in one patient and a double oesophagostomy (one cervical and one transabdominal) in three patients, digestive continuity being restored by colon interposition after spontaneous closure of the fistula in two.

One patient with caustic fistula died 5 weeks after the initial injury from concomitant severe caustic pneumonitis.

There exists no all-purpose recipe for the best management of a non-malignant oesophageal fistula in an adult patient. The assessment of the fistula and choice of the most relevant therapy should emerge from a multidisciplinary medicosurgical approach. Contrast oesophagography and fibreoptic bronchoscopy performed while the patient drinks methylene-blue-stained water are particularly valuable for settling the diagnosis. In most instances, closure of the fistula requires a specific surgical approach depending on the site of the fistula, the underlying disease and concomitant lesions.

Oesophagocoloplasty in the management of postcorrosive strictures of the oesophagus

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The clinical data, technical considerations, early and late postoperative complications and long-term results of 34 oesophagocoloplasties

Oesophagus

performed for 33 cases of postcorrosive oesophageal strictures between 1973 and 1990 have been analysed. All patients except one were older than 15 years of age.

The right colon with terminal ileum was used in 23 cases, the right colon alone was used in three cases and the left colon in eight cases. Major postoperative complications included necrosis of the transplanted colon in two cases, pneumothorax in seven cases, transient cervical anastomotic leakage in three cases, late stricture of the oesophageal anastomosis in one case and late stricture and transient fistulization from the cologastrostomy side in one case. Three patients died in the early postoperative period, a mortality rate of 9 per cent.

Benefits of using the right colon with terminal ileum include use of isoperistaltic bowel segment with an intact ileocaecal valve, which decreases the hazard of regurgitation from the colon, and an easier and safer anastomotic technique between ileum and cervical oesophagus.

Experimental endobrachyoesophagus: a preliminary report

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The induction of endobrachyoesophagus (Barrett's oesophagus) was achieved experimentally in dogs without prior oesophageal mucos-ectomy and following exposure to mixed gastric and biliopancreatic reflux. After two attempts to expose the oesophagus to these secretions by vertical jejuno-oesophagogastric anastomosis and Wedel oesophagogastric anastomosis had failed, a 100 per cent survival rate was achieved after Wedel oesophagogastric anastomosis with gastrojejunostomy.

This technique was applied in 14 beagle dogs (15–20 kg) of both sexes. Prior endoscopy (absence of oesophagitis), manometry (lower oesophageal sphincter location) and 24-h pHmetry (alkaline oesophagus and habitual absence of gastric basal acid secretion) were carried out. Following anaesthesia, intubation and midline lapar-

otomy, a Wedel oesophagogastric anastomosis with gastrointestinal anastomosis was performed, together with a gastroduodenostomy (3–4 cm vertically). A clip was left in place for radiographic referencing of the oesophagogastric junction. There were two deaths during anaesthesia, one due to late bowel loop necrosis, and one as a result of intestinal occlusion 2 months after surgery. The three instrumental explorations were repeated monthly in the same dogs, and a biopsy of the gastro-oesophageal junction (marked by a clip) and distal third of the oesophagus was taken in each case, for histopathological evaluation. Three dogs were killed after 1, 2 and 3 months to obtain a gastro-oesophageal strip evaluation of the limits of histopathological change.

The decreased lower oesophageal sphincter pressure resulting from surgical sphincter section was clearly reflected by manometry. pHmetry (1–7 months) revealed a significant increase in the duration of alkaline pH values (>8) 5 cm above the oesophagogastric junction.

	Mean(s.d.)	Student's t value	P
Oesophagus			
Preoperative	16.26(12.75)	} -3.2	0.033
Postoperative (1 month)	57.18(26.46)		
Stomach			
Preoperative	21.46(8.11)	} -3.0	0.037
Postoperative (1 month)	58.18(27.38)		

pH value >8

Endoscopically confirmed (1–7 months) distal oesophagitis (grades II and III) was noted, and confirmed by biopsy. The gastro-oesophageal strips revealed grades III and IV oesophagitis, and juxtapositioning of prism epithelium on oesophageal mucoglandular remains up to 1.5–2 cm from the referenced oesophagogastric junction. These findings suggested the onset of an endobrachyoesophagus.

Oesophagus: cancer

Surgical treatment of resectable oesophageal cancer

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Although total transposition of the stomach with cervical oesophagogastrostomy is considered the treatment of choice for resectable oesophageal cancer, many surgeons prefer an intrathoracic oesophagogastrostomy for tumours of the distal third of the oesophagus.

The results of a retrospective analysis of 26 consecutive patients with an epithelial cell carcinoma of the oesophagus who underwent oesophageal resection are reported. The male:female ratio was 24:2; median age was 51 (range 28–76) years. The tumour originated from the middle portion of the oesophagus in 11 (42 per cent) and from the lower portion in 15 (58 per cent) patients.

According to the tumour node metastasis classification, two (8 per cent) of the tumours were stage I, ten (38 per cent) were stage II and 14 (54 per cent) were stage III.

Cervical oesophagogastrostomy was performed in 13 (50 per cent) patients, and intrathoracic oesophagogastrostomy in 12 (46 per cent) patients; one patient died from massive intraoperative bleeding caused by direct tumour invasion of the myocardium. There were no postoperative deaths from dehiscence of the intrathoracic anastomosis.

The overall 1-year and 5-year survival rates were equivalent (25 per cent); for stage I and II patients ($n = 12$) it was 46 per cent and for stage III patients ($n = 14$) 0 per cent. The survival rate for patients undergoing cervical oesophagogastrostomy was 20 per cent and 33 per cent for patients undergoing intrathoracic anastomosis.

Survival after resection therapy for oesophageal carcinoma does not seem to be impaired by a decision to perform intrathoracic oesophagogastrostomy.

Combination therapy and surgery or surgery alone for oesophageal carcinoma: a randomized trial

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The advantages of combined therapy for oesophageal cancer are uncertain and can be determined only by the outcome of controlled trials. The preliminary results of a prospective randomized study in which chemotherapy and radiotherapy followed by surgical resection was compared with surgical resection alone are reported. Only patients under 76 years of age and without distant metastases were included in the trial. The adjuvant therapy regimen consisted of 5-fluorouracil (15 mg kg^{-1} daily for 5 days), cisplatin (75 mg m^{-2} on days 7 and 42) and radiotherapy to a total dose of 40 Gy over a 6-week period.

	Surgery ($n = 25$)	Surgery and combined therapy ($n = 18$)
Postoperative stage		
0–2a	5 (20)	11 (61)*
2b, 3	20 (80)	7 (39)*
Wall penetration	25 (100)	10 (56)†
Resolution of primary tumour	—	3 (17)
90-Day mortality	0 (0)	3 (17)

Values in parentheses are percentages. * $P < 0.01$ (χ^2 test); † $P < 0.001$ (Fisher's exact test)

Systemic toxicity from chemotherapy was minimal but while the difference in perioperative mortality rate did not reach statistical significance all three perioperative deaths in the combined therapy group were from necrosis and leakage at the anastomosis. This is a cause for concern and may negate the potential advantage of tumour down-staging.

Place for palliative surgery for cancer of the oesophagus and cardia

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From 1984 to 1991, 90 patients underwent a palliative oesophageal resection or bypass operation for cancer of the oesophagus or cardia. Reasons for palliation were incomplete tumour resection, the presence of non-resectable metastatic lymph nodes or the intraoperative evidence of liver or lung metastases.

The quality of life of 52 patients suitable for detailed follow-up was graded into four levels: I, normal activity; II, restricted activity outside the home; III, need for home assistance; IV, need for hospital assistance. Patients were classified into three categories by their alimentary comfort: A, comfort similar to that having existed before initial oesophageal symptoms; B, discomfort not requiring regular instrumental therapy; C, discomfort requiring regular instrumental therapy.

The 30-day and in-hospital mortality rates of the whole group were 1 and 2 per cent respectively. Median postoperative stay was 22.3 days with a median survival of 9 months. Quality of life was graded I for 13 (26 per cent) patients, II for 17 (35 per cent), III for 12 (24 per cent) and IV for seven (12 per cent) patients. Alimentary comfort was classified A in 24 (49 per cent) patients, B in 16 (33 per cent) and C in nine (18 per cent) patients.

We conclude that surgery may be justified in the palliative management of advanced cancers of the oesophagus and cardia because postoperative mortality is low, except in the terminal course of the disease, hospital assistance is not required for most patients and in more than four-fifths of cases dysphagia is prevented without need for regular instrumentation.

Endoscopic microsurgical dissection of the oesophagus in the treatment of oesophageal carcinoma: technique and clinical results

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To avoid the invasive procedure of oesophageal resection through thoracotomy, blunt dissection of the oesophagus followed by cervical oesophagogastrostomy is widely accepted in the treatment of oesophageal malignancy. However, complications such as uncontrollable bleeding and injury to the trachea or to the left recurrent nerve can occur. To minimize these complications of the blind procedure, we have developed the minimally invasive procedure of endoscopic microsurgical dissection of the oesophagus (EMDO), and started clinical use in 1989. EMDO, performed with a specially developed operating mediastinoscope, made it possible to combine the minimal invasiveness of the blunt dissection and the precision of the thoracic procedure. Without thoracotomy, the oesophagus can be removed with its surrounding structures preserved. Even regional lymph node dissection is possible. To date, EMDO has been performed in 30 patients with oesophageal malignancy. The hospital mortality rate was <10 per cent, which is not attributable to the endoscopic procedure. The mean blood loss in the endoscopic part of the procedure was <100 ml and the mean operating time was 200 min.

Five-year survivors after radical operation for oesophageal carcinoma: influence of pathological findings

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The aim of this work was to study 5-year survivors after radical resection for oesophageal squamous cell carcinoma and to compare the pathological findings with those of patients dying between 1 and 4 years after operation (control group). From 1979 to 1985, among 195

patients operated on, 30 (15.4 per cent) patients were alive 5 years after operation. There were 28 men and two women (mean(s.e.m.) age 57.5(8) years). Six patients had perioperative medical treatment (radiotherapy and/or chemotherapy). Tumour was located in the upper ($n = 4$), middle ($n = 9$) and lower regions ($n = 15$) respectively. Oesophagectomy with mediastinectomy and coeliac node dissection was performed in 28 cases; in two cases oesophagectomy without thoracotomy was performed.

Mean(s.e.m.) survival rate was 73(18) (range 60–147) months. Twenty-three patients were asymptomatic while seven symptomatic patients presented with reflux ($n = 3$), dysphagia ($n = 1$) and postprandial epigastric pain ($n = 3$). One patient presented with lung and liver metastases; four patients had an associated cancer during follow-up: tongue ($n = 1$), lungs ($n = 2$), gastropathy ($n = 1$). Of the 30 survivors, 11 presented with lymph node metastasis (nine juxtatumoral, one cervical and one cardiac). Of 195 patients, 88 presented without node invasion and 19 survived more than 5 years (22 per cent); 107 had positive nodes and only 11 survived more than 5 years (10.3 per cent). Cellular reaction within the tumour (i.e. lymphocytes and polynuclear leucocytes) and absence of fibrotic stroma within tumour were associated with good prognosis. These results must be confirmed; however, they suggest a potential role for adjuvant treatment in poor-risk patients.

Among 5-year survivors, no patient presented visceral or coeliac node metastasis, or a positive node with capsular rupture. On the other hand, other reported poor-risk criteria were observed (i.e. tumour >10 cm, cardiac or cervical nodes positive). Functional results are good with two-thirds of patients being asymptomatic. Four patients (13 per cent) presented with associated cancer, demonstrating the importance of long-term follow-up. Systematic mediastinectomy and extensive coeliac node dissection systematically performed during oesophagectomy could explain why 11 patients (37 per cent) with positive nodes were alive 5 years later.

Pharyngo-oesophageal reconstruction using gastric pull-up or colon interposition: management of complications

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Malignancies of the hypopharynx and cervical oesophagus are treated mostly by pharyngolaryngo-oesophagectomy and gastric pull-up (GP) or colon interposition (CI). Complications are frequent and may be serious, requiring additional surgical procedures. Our experience is reported herein: from 1980 to 1990, the pharyngo-oesophageal defect was reconstructed using GP in 95 cases and CI in 11.

Anastomotic leaks, including both clinical and radiological ones, were 22 (23 per cent) in GP and two (18 per cent) in CI. After GP, 19 leaks were managed conservatively (four deaths), and three were reoperated on (one death) as follows: reanastomosis, T tube drainage plus delayed skin flap repair, and partial stoma in a patient who died before skin flap repair. After CI, two leaks were successfully managed: one conservatively, and one with a partial stoma plus delayed skin flap repair. Segmental or total necrosis of the oesophageal substitute occurred in ten (11 per cent) GPs, and two (18 per cent) CIs. After GP, eight patients were treated with a partial stoma plus delayed skin flap repair (four deaths), one underwent successful take-down of the stomach plus CI and one died after the establishment of cervical stomas plus delayed free jejunal autograft and skin flap repair. After CI, both the patients died after colon loop take-down and the establishment of cervical and abdominal stomas.

Anastomotic strictures developed in eight patients after GP: seven were dilated successfully, and one required repair of the anastomosis.

The following intraoperative complications, which required additional surgical procedures, occurred. In a patient with the stomach too short to reach the pharynx, two temporary cervical stomas were performed; he died from recurrence before reconstruction. A patient with the azygous vein torn during transhiatal oesophagectomy required transthoracic haemostasis. A patient with CI showed defective venous drainage requiring a venous microanastomosis in the neck. In a patient undergoing GP, the right gastroepiploic vessels were torn so that a CI had to be performed. In a patient undergoing CI, a segmental necrosis of the colon was noted: the necrotic segment was resected, the colon was transposed subcutaneously, and a free jejunal autograft was performed to cover the gap between the pharynx and the colon, leaving a temporary

partial stoma at the jejuno-colic anastomosis. A patient with chylothorax underwent duct ligation.

In conclusion, after pharyngo-oesophageal reconstruction most anastomotic leaks can be managed conservatively by means of drainage, nasogastric tube insertion, parenteral or enteral nutrition, and broad-spectrum antibiotics. Reoperation is deemed necessary on the basis of clinical course. Conversely, reoperation is mandatory in the case of necrosis. Reoperations consist mainly of a temporary partial stoma in the neck and delayed skin flap repair after 3 weeks.

Anastomotic healing of the cervical oesophagus: effect of timing of radiotherapy

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A shorter interval between surgery and radiotherapy may be preferable to the 4–6-week interval currently favoured but the optimum interval for wound healing is unknown. This study examined the effect of different intervals between surgery and radiotherapy on oesophageal wound healing. A transverse incision through half of the cervical oesophageal circumference was repaired using three interrupted 6/0 Prolene sutures in female Wistar rats. Radiotherapy (37.5 Gy) was delivered to the cervical oesophagus ($n = 18$) at 1 week (group 1), 3 weeks (group 2) and 6 weeks (group 3). Healing was assessed 1 week after radiotherapy by clinical and histological criteria and bursting strength, and compared with that in control groups ($n = 13$) at similar intervals.

	Bursting strength (mmHg)		Histological score	
	Treated	Controls	Treated	Controls
Group 1	520(10.4)	540(12.3)	6.3(0.24)	0.76 (0.20)*
Group 2	510(12.2)	552(11.6)	6.1(0.17)	0.38(0.14)*
Group 3	575(13.2)	554(12.1)	5.5(0.13)	0.33(0.14)*

Values are mean(s.e.m.). * $P < 0.001$ versus treated (Wilcoxon rank sum test)

Radiation changes were similar in the treated groups. Free perforation occurred in two animals in group 1, and two in group 2. There was no difference in bursting strength between treated groups and controls. Wound healing was similar regardless of radiation timing. These results suggest that a shorter interval between surgery and radiotherapy may not adversely affect anastomotic healing.

Five-year survival after resection of the oesophagus for cancer

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From 1984 to 1990, 123 patients underwent subtotal oesophageal resection for cancer of the thoracic oesophagus. Cancers of the cardia treated by oesophagogastricectomy and jejunal interposition were not included in this series. Digestive continuity was restored by gastric pull-up to the neck in 119 patients and colon interposition in four. Thirty-day and hospital mortality rates were none and 2.4 per cent (3 of 123), respectively. Resection was macroscopically incomplete in 32 patients (26 per cent) owing to involvement of the oesophageal margin (one), liver, lung or thyroid metastases (six), tracheo-bronchial or aortic involvement (11), non-resectable lymph nodes (12), and lack of node dissection in two elderly patients. The survival rate after incomplete resection was 41.2 per cent at 1 year, 3.4 per cent at 2 years and none at 3 years. Crude and actuarial survival rates for the 91 patients in whom resection was macroscopically complete were 84.1 per cent and 79.5 per cent at 1 year, 50.5 and 45.1 per cent at 3 years and 41.6 and 34.5 per cent at 5 years, respectively. The 5-year crude survival rate was 60 per cent for tumours that extended into but not through the muscularis propria, 21 per cent for those that invaded the full thickness of the wall, 60 per cent for those without regional lymph node involvement, 21 per cent for those with metastatic lymph nodes, 31.8 per cent for squamous cell carcinomas and 33 per cent for adenocarcinomas. The 5-year actuarial survival

rate was 40.9 per cent for the 24 patients who were submitted to adjuvant radiotherapy versus 43.4 per cent for those treated by surgery alone.

The study shows that 5-year survival rates similar to those reported by Japanese teams may be achieved in Caucasian patients after extensive oesophageal resection. Prognosis depends on the node involvement and the depth of wall penetration. It is not related to the histological type of the tumour, and is not improved by adjuvant radiotherapy. The usefulness of extensive lymph node dissection is emphasized by the 21 per cent crude survival rate achieved at 5 years in patients with metastatic regional nodes.

Contribution of thoracoscopy in oesophageal resection

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In the treatment of oesophageal neoplasia, we employ the Santy-Lewis procedure. Since May 1991 we have performed five oesophagectomies for neoplasms where thoracostomy was replaced by thoracoscopy.

Patients comprised three men and two women, with a mean age of 62 years, all affected by primary tumours of the oesophagus. In four cases the tumour was located in the middle third of the oesophagus, and in the other case it was located in the upper third. All patients were subjected to thoracoscopy, the mean duration of which was 180 min.

Thoracoscopy allowed complete mobilization of the oesophagus in four patients. The patient whose tumour was considered irresectable by imaging techniques underwent complete oesophagectomy. One patient with a small tumour in the middle third of the oesophagus underwent digital mobilization through an abdominal approach to free neoplastic adhesions to the pericardium. None of the patients died. The only perioperative complication was the necessity for intermittent pulmonary re-expansion owing to venous desaturation. There were no postoperative infectious pulmonary complications. One patient developed an anastomotic fistula in the neck which healed with parenteral nutrition.

In conclusion, primary thoracoscopy for the treatment of oesophageal neoplasia gives information regarding the true local stage of the disease without the necessity of thoracostomy and its attendant complications. The mobilization of the oesophagus by thoracoscopy seems to be superior to other types of closed thoracic procedure and complications due to thoracotomy are avoided.

Thoroscopic oesophageal resection: an experimental study in the pig

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Following earlier experimental studies of laparoscopic abdominal vagotomy and Nissen fundoplication in the pig, a thoroscopic approach to oesophageal surgery has been developed. Four pigs

weighing 20–30 kg were anaesthetized and turned on their left side for a right transthoroscopic procedure. Four or five trocars were needed. The consequent pneumothorax was well tolerated and allowed the omission of carbon dioxide insufflation. A gastric tube was placed as a guide to aid dissection. The lung was retracted anteriorly and the mediastinal pleura was opened from below using a hook electrode. The azygos vein was ligated with clips and divided. The mediastinal lymph nodes could be resected without difficulty. Despite appropriate mobilization, the stomach did not reach the neck easily. Therefore, reconstruction was achieved by intrathoracic or cervical oesophagogastric anastomosis. The gastric stump was constructed by an open laparotomy and stapling technique. Total oesophagectomy and gastric replacement in two animals and partial oesophagectomy with intrathoracic oesophagogastronomy in two other animals have been performed successfully in this department. In human surgery, several advantages of the thoroscopic approach can be expected: less respiratory distress and postoperative pain than in open thoracotomy, better control of haemostasis and more adequate exposure of the cancer than in the transhiatal approach. This remains to be confirmed.

Effect of erythromycin on emptying of the denervated stomach

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Oesophagectomy necessitates total gastric vagotomy and is associated with delayed gastric emptying. Cisapride and erythromycin have both been shown to improve gastric emptying in the innervated stomach. Their effect on the postoesophagectomy stomach is unknown. A 4-h study using 25 g technetium-99m tin colloid labelled egg white and 100 g of indium-111 DTPA labelled orange juice examined the rate of emptying of solids and liquids. Studies were carried out 2 months after three-stage oesophagectomy with preservation of the whole stomach. Group 1 had resection without pyloroplasty. Group 2 were studied after 3 days of cisapride treatment and group 3 were studied after 3 days of erythromycin therapy.

Operation	Mean(s.e.m.) percentage remaining at 4 h
Group 1 Resection (no pyloroplasty) (n=16)	56(6.8)
Group 2 Resection and cisapride (n=10)	50(11.6)
Group 3 Resection and erythromycin (n=6)	18(9.2)*

* $P < 0.01$ versus controls (Mann-Whitney *U* test)

Cisapride did not improve emptying of the postoesophagectomy stomach. Erythromycin provided a significant improvement in the rate of gastric emptying and may have a role in the treatment of problems from gastric stasis following oesophagectomy and in the denervated stomach.

Oesophagus: reflux

Effects of an acid milieu on healing in a canine Barrett's oesophagus model

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The evidence for regression of columnar epithelium in Barrett's oesophagus remains controversial. In order to study the phenomenon experimentally we established a reversible canine reflux model in which mucosal strip defects were created in the lower oesophagus, 1 cm proximal to the gastro-oesophageal junction. Reflux was ensured by creation of a Wendel cardioplasty and acid stimulation by pentagastrin (100 µg daily). The healed strip was excised at 3 months. Regeneration, in the presence of acid reflux, was by columnar epithelium in seven of ten dogs.

After re-creation of the mucosal defect, reversal of the reflux-inducing procedure, and omeprazole therapy (20 mg daily), a mixed pattern of columnar regeneration with islands of squamous cells occurred in all six animals studied. Histologically the regenerating epithelium was shown to arise from the oesophageal gland ducts, the upper third of which are lined with squamous epithelium and the lower two-thirds with columnar or cuboidal cells.

It is suggested that when mucosal healing occurs in the presence of acid reflux, columnar regeneration predominates, but when reflux is controlled, squamous regeneration may occur provided the squamous lining of the oesophageal gland ducts is preserved.

Oesophageal manometry in the surgical treatment of gastro-oesophageal reflux disease

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Although it is generally agreed that clinical features and pH-metric tests are of paramount importance in the diagnosis of gastro-oesophageal reflux disease (GORD), manometry can also provide valuable information. Manometry confirms the diagnosis and excludes other motor disorders of the oesophagus.

We have regularly used manometry (using standard low compliance equipment and an open tip catheter). GORD is associated with low lower oesophageal sphincter (LOS) pressure and a short high pressure zone, but these indices are not well correlated with the severity of oesophagitis. In all patients with GORD selected for surgery the LOS pressure was low (mean 7 mmHg, measured by station and rapid pull-through techniques). The sphincter was short in all cases, <2 cm, and the intra-abdominal part absent or very short (<1 cm).

The preferred operation was a Nissen fundoplication with intraoperative neo-LOS pressure control (mean values about 25 mmHg). This pressure is known to reduce over the 6–12 months after operation, but the neo-LOS antireflux function persists.

Manometry is a well tolerated and simple technique. In our opinion manometric data are essential for the optimal surgical management of GORD.

Clinical, radiological and functional results of remedial antireflux operations

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Fifty-five patients who did not receive the symptomatic relief expected after primary surgery for gastro-oesophageal reflux disease underwent remedial surgery. Presenting symptoms were heartburn alone (27), heartburn and dysphagia (ten), dysphagia alone (nine), chest pain (four), left shoulder pain (one), left shoulder pain and fever (one), and signs of anaemia (three). The symptom of dysphagia was usually of immediate onset, whereas heartburn recurred after a symptom-free period ($P = 0.008$). The most common failed antireflux procedure was a Nissen fundoplication (37 patients). The incompleteness of the residual wrap, its location around the stomach and irreducibility of the gastro-oesophageal junction below the

diaphragm were accurately predicted by barium swallow study in 70, 83 and 92 per cent of patients, respectively. Abnormal oesophageal body motility was related to oesophagitis, herniation of the residual repair into the chest, or both (16 of 20). Oesophageal acid exposure and prevalence of oesophagitis were more common in patients with heartburn than in those with other symptoms ($P < 0.02$). Intraoperative findings were breakdown of the repair, its location around the stomach, its herniation into the chest, excessive tightness, gastric fistula, or any combination of these. Remedial surgery consisted of a new antireflux procedure (42 patients), a new antireflux procedure and closure of a gastric fistula (three), closure of gastric fistula alone (one), closure of the crura (four), oesophageal resection (three), total gastrectomy (one) and duodenal diversion (one).

Postoperative mortality and morbidity rates were 5.4 and 23.4 per cent, respectively. At follow-up, clinical, radiological and pH-monitoring success rates were 89.1, 85.7 and 88.4 per cent respectively. The study emphasizes the necessity of healing oesophagitis by antacid therapy before remedial surgery, and the usefulness of extensive preoperative evaluation of the anatomy and function of the foregut; it identifies the technical steps required for such specialized surgery to succeed.

Cervical manifestations of gastro-oesophageal reflux

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The aim of this study was to assess the importance of gastro-oesophageal reflux in chronic laryngitis, globus sensation and upper oesophageal sphincter (UOS) spasm using modern methods of recording oesophageal acid exposure times (AET). Prolonged ambulatory pH monitoring was used, together with UOS manometry, endoscopy and biopsy of the distal oesophagus and posterior larynx, to investigate 97 patients with suspected acid laryngitis and 87 patients with globus sensation. The results were compared with those in 54 control subjects.

In the laryngitis group, 24 patients had normal AET and oesophageal biopsy but all had interarytenoid laryngitis or parakeratosis. In 56 patients both biopsies were normal; 14 of these had significantly elevated total, upright and recumbent AET. Laryngeal pathology was found in association with prolonged AET or distal oesophagitis in only 17 patients. In 23 per cent of the globus patients, total AET was prolonged above the mean plus two standard deviations of the normal control group. A few patients had distal oesophagitis but none had an acute inflammatory infiltrate. Finally, AET was not significantly correlated with UOS pressure, which also failed to show any augmentation during upper oesophageal acid infusion in 17 subjects. Recent reports appear to have greatly overestimated the importance of gastro-oesophageal reflux in the aetiology of cervical symptoms.

Evaluation of the Watson fundoplication

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Conventional surgical treatment for gastro-oesophageal reflux (GOR) results in 10–20 per cent of patients suffering from often disabling side-effects of the operation such as gas-bloat. A recently described operation for GOR (Watson fundoplication), reported to have fewer side-effects, was assessed. The operation consists of a posterior crural repair, anchoring of the oesophagus to the crura and a 120° fundal wrap¹.

A group of 34 patients with GOR, unresponsive to medical therapy, was studied with preoperative and postoperative 24-h ambulatory pH monitoring. The results were expressed as DeMeester scores. All patients were recently interviewed by an independent observer. The median length of follow-up was 34 (range 8–52) months.

The mean preoperative DeMeester score was 84 and this was reduced to a mean of 16 after operation, representing a mean individual reduction of 66.7 ($P < 0.001$, Student's paired t test). Of the patients 31 of 34 (91 per cent) were graded as Visick grade 1 or 2

and three as Visick 3. Two poor results were due to recurrent GOR and one was due to moderate dysphagia. These symptoms were adequately controlled by medical means. None of the patients suffered gas-bloat.

This preliminary study demonstrates that the Watson fundoplication is both effective in controlling GOR and has a low incidence of side-effects.

1. Watson A, Jenkinson LR, Ball CS, Barlow AP, Norris NL. A more physiological alternative to total fundoplication for surgical correction of resistant gastro-oesophageal reflux. *Br J Surg* 1991; 78: 1008-94.

Nissen-Toupet procedure for gastro-oesophageal reflux: a prospective study of 24 cases

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The Nissen procedure is an effective treatment for gastro-oesophageal reflux but induces some specific complications (ulcers, transhiatal migration, slipped Nissen). The Toupet procedure does not induce these complications but is less effective. In order to preserve only the advantages without the drawbacks of both procedures a combined technique was tried. The aim of this prospective study was to evaluate this procedure.

The operative technique consisted of performing a suture of the crura, a posterior hemifundoplication, fixed to the crura and completed by a short (1-2-cm) circular fundoplication. Twenty-four patients (12 men and 12 women) of median age 56 (range 25-74) years were operated on. All the patients had clinical signs of gastro-oesophageal reflux; endoscopy showed oesophagitis in eight cases. The evaluation involved clinical history, endoscopy, 3h postprandial pH test and oesophageal manometry; it was performed before surgery and later. The mean(s.e.m.) follow-up was 28.9(8.9) (range 18.6-44.4) months.

There were only two benign postoperative complications; none of the Nissen-specific complications was observed. Clinical signs of reflux and oesophagitis disappeared in all cases. All the patients were able to belch, but five of them who felt sick could not vomit. Slight dysphagia was present in three patients. Patients found the result very good in 21 cases and good in three. The mean percentage of time at pH < 5 was less than 10 per cent in 23 patients; its mean(s.e.m.) value was 44.6(21.9) (range 10-100) per cent before surgery and 1.3(2.8) (range 0-12) per cent after ($P < 0.001$). The mean(s.e.m.) lower oesophageal sphincter pressure was 11.5(6.1) (range 3-23) cmH₂O before surgery and 17.9(5) (range 11-30) cmH₂O after ($P < 0.01$). The mean(s.e.m.) velocity of oesophageal waves was 1.8(0.4) (range 1.2-2.8) cm s⁻¹ before surgery and 2.4(0.9) (range 1.4-5.5) cm s⁻¹ after ($P < 0.05$).

In conclusion, this procedure provides an effective treatment for gastro-oesophageal reflux and an improvement of oesophageal motility and prevents the complications related to the Nissen procedure, except the inability to vomit.

Prospective assessment and importance of the length of a 360° fundoplication

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Twenty-three patients with gastro-oesophageal reflux disease underwent a 'loose Nissen' procedure and were studied with a 1-year follow-up. The patients (13 men, ten women) had a median age of 55 (range 28-75) years. None had oesophageal stenosis and approximately 50 per cent had associated pathology (eight cholelithiasis; four duodenal ulcer). The patients underwent preoperative and postoperative studies consisting of clinical assessment, barium transit, endoscopy, 24-h pH recording, manometry and radionuclide transit. None had reflux symptoms after operation, 13 per cent of cases had dysphagia and 4 per cent had gas-bloat syndrome. The barium transit demonstrated only one case (4 per cent) of incomplete sliding hernia. A 24-h pH recording showed two cases (9 per cent) with signs of reflux. Manometry revealed a near doubling of the lower oesophageal sphincter pressure from 14 to 27 mmHg at the 3-month

control, persisting at 25 mmHg at the 1-year control study. Radionuclide transit showed delayed transit in patients with dysphagia. Patients with a radiological fundoplication >4 cm in length had a greater residual activity of the isotope in the oesophagus. Patients with dysphagia had a fundoplication >4 cm in length. Those with more than 10 per cent retention during the first minute after swallowing had a significantly increased lower oesophageal sphincter pressure and a longer radiological fundoplication.

In conclusion, loose Nissen fundoplication gives good results in gastro-oesophageal reflux disease but should be no longer than 4 cm.

Angelchik prosthesis in the surgical therapy of reflux oesophagitis

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The authors refer to experience acquired from 1981 to 1985 using the Angelchik prosthesis in 22 patients with gastro-oesophageal reflux oesophagitis resistant to medical therapy for more than 6 months.

Clinical evaluation used Visick's scale, as modified by Deakin. Monitoring took place 1 month, 12 months, 5 years and 10 years from operation. Intraoperative mortality and morbidity rates were zero. Complications were transient dysphagia in four cases, persistent dysphagia in three cases, transient gas-bloat syndrome in one case and prosthesis displacement in six cases.

Clinical results were satisfactory only in patients with a short period of follow-up (30 days): Visick grade 1 and Visick grade 2 with a rate of 91 per cent. This success rate was reduced to 84 and 67 per cent in patients with a follow-up of 1 year and 5-10 years, respectively.

The authors conclude that the Angelchik prosthesis should be employed in a limited number of cases and reserved for elderly, obese and high-risk patients.

Ten years of experience in the treatment of gastro-oesophageal reflux

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Between 1981 and 1990, 144 patients were operated on for gastro-oesophageal reflux. There were 76 (52.8 per cent) women and 68 (47.2 per cent) men. Patient age ranged from 16 to 78 (mean 49) years. Twenty patients (13.9 per cent) had achalasia. In 124 patients the gastro-oesophageal reflux was secondary: to a sliding hiatus hernia in 119 (82.6 per cent) and to some other oesophageal disease in five (3.5 per cent) such as paraoesophageal cyst, diverticulum of oesophagus or leiomyoma.

Before surgery, radiography, endoscopy, biopsy, and isotopic examinations were performed. In the early cases, Nissen fundoplication was performed in 14 patients and since 1982 Nissen with Rossetti modification has been undertaken in 130. In a total of 41 patients (28.5 per cent), an antireflux procedure was combined with cholecystectomy in 22, gastrectomy in seven, vagotomy in two, nephrectomy in one, splenectomy in three and other procedures in six.

On the basis of the postoperative follow-up it was noted that in 80 per cent of patients the Nissen-Rossetti fundoplication completely eliminated the subjective symptoms. Four patients (2.8 per cent) needed reoperation: two because of ulceration in the antireflux cuff and one because of suture separation. In one case paraoesophageal hernia occurred because of a wide unsutured oesophageal hiatus.

We examined 57 patients 1-8 years after the operation. In 42 patients radiographic examination was normal; 39 patients had normal endoscopy and 37 had normal isotopic scanning. The biopsies showed pathological changes in 31 patients (54 per cent); 22 (39 per cent) had reflux oesophagitis including 17 of Barrett's type. Poorer postoperative results were noted in women in all the diagnostic examinations.

It is concluded that the Nissen-Rossetti fundoplication improves antireflux function in about 80 per cent of patients. The histopathological changes persist in over 50 per cent of the patients although there are no symptoms. These patients should be regarded as a high-risk group and require periodic follow-up.

Heller's cardiomyotomy should be combined with an antireflux procedure

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Between 1973 and 1990, 62 patients were operated on for achalasia of the oesophagus. There were 28 (45 per cent) women and 34 (55 per cent) men aged 16–76 years. The typical duration of symptoms varied from 3 months to 26 years. The modified Heller's operation (anterior cardiomyotomy) was the only procedure performed up to 1981 in 21 patients. From 1982, the anterior cardiomyotomy was accompanied by Nissen–Rossetti fundoplication from the abdominal approach in 41 patients. The thoracic approach was used in patients requiring reoperation in four cases of insufficient myotomy of the oesophageal layer. Before operation radiographic examination of the upper alimentary tract and endoscopy and biopsy of the mucosa of the lower part of the oesophagus were carried out.

The long-term results of the operative treatment were evaluated in two groups of 13 patients: group I operated on between 1973 and 1981 (modified Heller's operation) and group II operated on between 1982 and 1986 when the anterior cardiomyotomy was combined with Nissen–Rossetti fundoplication. The average follow-up time in group I was 9.3 years, in group II 3.3 years. Special attention was paid to the occurrence of gastro-oesophageal reflux. From the history five (38 per cent) patients in group I and one (8 per cent) in group II reported reflux. On radiography, contrast reflux from the stomach to the oesophagus was found in three (23 per cent) group I patients and in none of group II. Oesophagitis was proved at endoscopy in nine (69 per cent) patients in group I and in two (15 per cent) in group II. During isotopic scanning, gastro-oesophageal reflux was noted in nine (69 per cent) of group I and in eight (62 per cent) of group II. On microscopic examination all group I patients and four (31 per cent) group II patients revealed oesophagitis and paraepidermoidal changes of the oesophageal mucosa. Statistically significant better treatment results were noted in group II.

Most patients subjected to a modified Heller's operation had oesophagitis of the lower oesophagus at follow-up. Heller's operation should be combined with an antireflux procedure.

Long-term results of antireflux surgery

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Antireflux surgery provides relief of symptoms in 85–90 per cent of patients but few long-term reports on outcome are available. Ninety patients had antireflux surgery between 1977 and 1986. Sixty had a Rosetti–Hell fundoplication; 32 of these were part of a randomized trial and compared with 28 Angelchik prostheses. At the time of the study 13 patients had died, eight were lost to follow-up and 69 were available for assessment (mean follow-up 99 (range 61–198) months). Subjective assessment was by a modified Visick score and objectively by upper gastrointestinal endoscopy and pH monitoring.

	Overall		Randomized trial	
	Preop.	Postop.	Angelchik	Rosetti–Hell
Visick 1 and 2	–	78 (54 of 69)	82 (18 of 22)	88 (22 of 25)
Hiatus hernia	74 (45 of 61)	3 (1 of 39)*	0 (0 of 13)	6 (1 of 16)
Oesophagitis	89 (54 of 61)	18 (7 of 39)*	23 (3 of 13)	19 (3 of 16)
Normal acid score	23 (7 of 31)	70 (21 of 30)*	70 (7 of 10)	67 (10 of 15)

Values are percentages (numbers of patients). *P < 0.001

The mean DeMeester acid score was reduced from 39.4 before operation to 14.5. The controlled trial showed no significant difference between the groups in terms of symptoms, DeMeester (acid) score or oesophagitis but three prostheses had to be removed because of complications. Patients with Barrett's mucosa (n = 7) all improved clinically but none had evidence of regression. Antireflux surgery provides lasting control of reflux and it retains an important role in the era of acid-blocking agents.

Results of surgical treatment in 65 patients with reflux-induced oesophageal strictures

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From 1976 to 1990, 65 patients (39 men, 26 women; mean age 50 years) underwent surgery for reflux-induced oesophageal strictures. Ten patients had had previous operations (four antireflux procedures, three vagotomies and pyloroplasties, two partial gastrectomies, one Heller's myotomy). Eleven patients had Barrett's oesophagus and scleroderma was diagnosed in nine. In all, 38 patients had undergone an average of three endoscopic dilations (range one to eight). The mean length of the stricture was 2.6 cm.

Primary treatment consisted of fundoplication in 46 patients (71 per cent), oesophageal resection in 15 (23 per cent) and total duodenal diversion in four (6 per cent). The fundoplication wrap was partial in 32 patients, total in 14, and combined with a Collis gastroplasty in ten. Oesophagectomy was performed without thoracotomy in five patients. The continuity of the alimentary tract was re-established using the colon (n = 9), stomach (n = 4) or jejunum (n = 2). The mortality rate was 5 per cent, including two anastomotic leaks and one acute pancreatitis. Two patients with anastomotic leak healed conservatively (morbidity rate 3 per cent). The need for subsequent dilations was markedly reduced in patients undergoing fundoplication, since only three patients were further dilated after the first year of follow-up. Overall, six patients (9 per cent) required reoperation. Five patients with persistent dysphagia after partial fundoplication underwent oesophageal resection and reconstruction using colon (two), stomach (two), or jejunum (one). Oesophagectomy was performed without thoracotomy in two patients. One patient with severe reflux symptoms after partial fundoplication underwent total duodenal diversion. There was no mortality and one anastomotic leak healed conservatively. A total of 42 patients was followed for 12 to 120 months after surgery (mean 46 months). Of these patients, 34 (81 per cent) had Visick grade 1–2.

We conclude that primary antireflux surgery may favourably influence the natural history of oesophageal strictures by reducing the need for subsequent dilations. To achieve this goal, surgical treatment should be undertaken early in the course of the disease to avoid progressive transmural fibrosis, oesophageal shortening, and further functional damage secondary to repetitive dilations.

Physical training and gastro-oesophageal reflux

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The principal aim of this study was to determine whether physical training can cause gastro-oesophageal reflux (GOR) in asymptomatic subjects and increase it in patients with proven gastro-oesophageal reflux disease (GORD). A subsidiary aim was to see whether GOR is more probable in both groups of subjects when physical training is performed after meals.

A total of 24 subjects (12 with GORD and 12 asymptomatic) was studied. All were subjected on two different non-consecutive days to prolonged oesophageal pH monitoring. During the first day the patients were controlled for two periods, each of 3.5 h. During this time the patients rested. The two periods were interrupted by a break of 1 h for lunch. During the second day the two periods were interrupted 1 h after the start by 30 min of physical training. At the end of the test the duration of exposure of the oesophagus to acid and the number of episodes of reflux in the different periods of the study were calculated and the values of the parameters obtained on the 2 days were compared separately. Crossed comparisons between the data recorded while fasting and after eating were also made. Increases were seen in both groups particularly after meals.

	Asymptomatic subjects			Patients with GORD		
	Day 1	Day 2	Increment (%)	Day 1	Day 2	Increment (%)
Mean duration of acid exposure (min)	19	43	5.7	138	193	13.1
Mean no. of GOR episodes	15	37	5.2	120	136	3.8

The pH values showed that, in both groups of patients after physical training, an increase occurred in the duration of exposure of the oesophagus to acid and the number of episodes of GOR compared with normal conditions, especially in the postprandial period. The effect of physical training on the onset of GOR suggests that patients with GORD should not practise physical or sporting activities to excess, nor have meals immediately before physical or sporting activities.

Lower oesophageal sphincter oblique fibre response to axial traction: experimental and clinical intraoperative manometric data in healthy controls and refluxers

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Studies by Christensen have shown an enhanced dose-response effect when traction is exerted on the smooth muscle fibres of the lower oesophageal sphincter (LOS). In turn, Stelzner described the intercrossed oblique nature of these LOS fibres, forming a structural mesh or network; this suggests that axial oesophageal traction on the cardia or stomach would narrow this distal oesophageal segment and

raise its pressure. Since 1971, intraoperative manometry has enabled us to observe that patient LOS recovers pressure when subjected to traction. In 1972 we evaluated the dose-response effect of successive contractions on three parameters in ten dogs: high pressure zone length, mean pressure and area (defined as the millimetre sum of heights from each millimetre of baseline to the pressure tracing). Traction was increased stepwise up to 1 kg, after which the resulting curve was seen to flatten out.

In 1974 we started a prospective study of 62 patients without reflux oesophagitis (lithiasis, hernia, eventration) and 49 refluxers (as evidenced by clinical examination, endoscopy and brief pH testing), performing both intraoperative and postoperative manometry under continuous perfusion and 1 cm per 5 s extraction-inscription.

A clear dose-response effect to traction was noted; this effect was reflected by an ascending curve that flattened out after 1 kg traction. This response was found to be exclusive of the high pressure zone of the LOS. In both humans and dogs, area was found to be the most discriminating parameter.

In conclusion, Christensen's observations were confirmed that responsiveness of the oblique smooth fibres of the LOS is increased. It is important to note that the supposedly weak LOS of the refluxer responds as well to traction as do the healthy controls, with increases in all three depressed parameters to normal levels. Thus, rather than being weak, the LOS of the refluxer is weakened by the shortening of its oblique fibres as a result of the implicit cardia ascent.

Tissue inhibitor of metalloproteinases-1: a biochemical barrier to tumour invasion

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Tissue inhibitor of metalloproteinases-1 (TIMP-1) may regulate the proteolytic activity of those matrix metalloproteinase enzymes, such as type IV collagenase and stromelysin, which promote tumour invasion. Such a role has been suggested by *in vitro* studies in which the passage of malignant cells across artificial basement membranes was inhibited by exogenously applied TIMP-1.

The aim of this study was to investigate the presence and distribution of TIMP-1 by immunolocalization studies on frozen sections of normal and malignant tissue from 39 resected specimens of colorectal adenocarcinoma (Dukes' A, four; Dukes' B, 16; Dukes' C, 19). An indirect immunohistochemical technique employing sheep polyclonal antibodies raised against TIMP-1 was used.

There was a significant difference in the number of tumours expressing TIMP-1 at the tumour mucosal junction (TMJ) compared with the tumour centre, 25 and 11 cases respectively ($\chi^2 = 10.11$, $P < 0.01$). In eight patients TIMP-1 was present in the normal mucosa and in all of these patients TIMP-1 was also observed at the TMJ of the associated tumour. This differed significantly from the 31 patients whose normal mucosa was negative for TIMP-1; only 17 of these 31 patients had TIMP-1 identifiable at the TMJ ($P = 0.018$, Fisher's exact test). When present in both normal and malignant tissues, TIMP-1 was exclusively localized to endothelial cells.

The dominant presence of TIMP-1 at the TMJ suggests a regulatory role in tumour invasion which is more likely to occur if TIMP-1 is expressed by the normal mucosa.

Interleukin 10 gene transcription in renal cell carcinoma: a polymerase chain reaction study in tumour biopsies

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Most human tumours are infiltrated by lymphocytes. The functional nature of the interaction between lymphocytes and neoplastic cells is presently unclear. Lymphocytes have been shown to express activation markers such as HLA-DR, CD69 and CD45RO, but not CD25. Recently it has been reported that interleukin 10 (IL-10) is a powerful inhibitor of cytokine synthesis and that it might have an inhibitory role in immune responses.

Based on these reports the transcription of the IL-10 gene was investigated in freshly excised biopsies from tumour and healthy renal tissue, as well as in the simultaneously sampled autologous peripheral blood mononuclear cells (PBMC) from five patients with renal cell carcinoma (RCC). Sensitive polymerase chain reaction (PCR) techniques were used. RNA was extracted by the guanidine thiocyanate method and reverse transcribed. IL-10 transcripts were amplified by using specific primers in 35-cycle PCR.

In three of five patients with RCC IL-10 transcripts could be detected in tumour biopsies but not in the healthy renal tissue or in the autologous PBMC.

Although the cell type(s) transcribing the IL-10 gene cannot be identified with this technology, it is tempting to speculate that production of this cytokine might affect immune responsiveness against tumour cells.

Genomic analysis by flow cytometry and Southern blotting in colorectal cancer: preliminary results

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Many colorectal cancers have specific alterations in genomic material of uncertain significance. Fresh specimens of 20 colorectal cancers

have been analysed studying ploidy and DNA characteristics by flow cytometry (FCM) and detection of p53 gene by Southern blotting using EcoRI, BamHI and HindIII as restriction endonucleases.

Seven of the 20 were diploid and 13 were aneuploid. Mean (s.e.m.) distribution of nuclei according to the cell cycle phases (G0/G1, S, G2/M) was 82.3(8.2) per cent, 12.1(6.5) per cent and 4.6(2.5) per cent, respectively. Coefficient of variation, DNA index, DNA aneuploidy and proliferative activity showed no significant differences in any of the clinical parameters studied (age, sex, localization, preoperative carcinoembryonic antigen levels, Dukes' classification and histological grading). We have not found homozygotic deletion of p53 in any of the patients studied.

We conclude that ploidy seems to be an independent factor and that the pathogenesis of these tumours is not related to the presence of deletion at these levels.

Oncogene *her2/neu* in gastric carcinoma

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In a retrospective study, the biological and prognostic relevance of the *her2/neu* oncogene gastric carcinoma was studied.

The *her2/neu* oncogene product p185 was studied in 58 patients by immunohistochemistry using a polyclonal antibody. High molecular weight DNA of tumours and matched normal mucosa was available in 25 patients. This was digested with EcoRI, transferred on to nylon membranes by Southern blotting and hybridized with either a 420-base pair BamHI or a 1.45-kilobase EcoRI fragment of the *her2/neu* cDNA.

The oncogene *her2/neu* was found to be amplified in 20 per cent of the cases studied ($n = 5$; 16–24-fold). Two carcinomas showed additional gene rearrangement. Amplification was irrespective of the site and tumour stage (Union International Contra la Cancrum, 1987), but occurred only in intestinal-type carcinoma and correlated with the expression of p185. The oncogene product could be detected at the basal membranes in 38 per cent of the cases studied (22 of 58). Positive immunoreactivity was found in well and moderately differentiated tumours of the intestinal type, but not in poorly differentiated lesions or tumours of the diffuse type ($P < 0.01$). T₁ tumours had less membrane staining than advanced primary lesions ($P < 0.05$). Overall survival did not differ between cases positive and negative for p185. Multivariate analysis, however, defined patients who had undergone curative resection with stage III and IV disease among whom the patients positive for p185 had a poorer survival ($P < 0.05$).

In the multistep process of tumorigenesis, *her2/neu* amplification seems to be associated with intestinal-type gastric carcinoma. Overexpression of the gene product may help in identifying patients with a poorer prognosis.

Granulocyte macrophage-colony stimulating factor: studies in a tumour model

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Granulocyte macrophage-colony stimulating factor (GM-CSF) is a cytokine with established myelopoietic and potential antineoplastic effects. This study examined the effects of GM-CSF on host antitumour responses in a murine model.

In study 1, mice ($n = 40$) received Lewis lung carcinoma implants (10^6 tumour cells, subcutaneously), and were randomized to receive GM-CSF ($1 \mu\text{g day}^{-1}$) or saline control for 10 days, and studied for tumour volume. In study 2, peritoneal macrophages were harvested from mice ($n = 30$) and studied (with or without GM-CSF co-culture, 50 ng ml^{-1} per 10^6 cells) for macrophage antitumour mechanisms including oxygen free radical (O_2^-) production, nitric oxide (NO) release and non-opsonized phagocytic function (percentage macrophage ingestion of *Candida*).

	Study 1	Study 2		
	Tumour volume (ml)	O ₂ ⁻ (nmol)	NO (μmol)	Ingestion (%)
Control	3.5(0.7)	0.2(0)	10(2)	8(1)
GM-CSF	1.4(0.4)*	0.7(0)†	29(1)†	27(2)‡

Values are mean(s.e.m.). * $P = 0.02$; † $P < 0.01$; ‡ $P < 0.001$ versus controls

GM-CSF significantly up-regulated all macrophage antitumour mechanisms studied. *In vivo* administration of GM-CSF significantly decreased tumour growth after 10 days. This cytokine functions through the enhancement of macrophage tumoricidal activity. These novel findings suggest that GM-CSF may have a therapeutic role in the tumour-bearing host.

Totally implantable venous access systems: a new placement technique

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The use of totally implantable venous access systems for the treatment of patients with cancer has become a useful practice in recent years and at present this is a common technique in most of the oncological services. Different types of system, with their own specific characteristics and most usual methods of placement, may be encountered.

Central venous access can be achieved via several routes dictated by the presence of local pathology, anatomical abnormality or venous occlusion. One of the more common sites is the cephalic vein by direct surgical exposure (cut-down), but this vein is absent in some 10 per cent of subjects and may have thrombosed following prolonged peripheral venous therapy.

We describe here a surgical method that is being used in our service as a result of 6 years' experience with >185 implanted reservoir pumps. A 1-cm incision is made in the infraclavicular fossa, through which, by direct subclavian vein puncture, a catheter is placed and advanced into the superior vena cava. The skin incision is then enlarged by 3 cm to develop a subcutaneous pocket. The chamber is sutured to the muscle fascia. The entire procedure is carried out with 5–10 ml local anaesthetic and the mean duration of the operation is 15 min.

This technique, of great technical simplicity, is particularly useful if radiological screening facilities are not available; it can be performed in a minor surgery theatre.

Immunological responses induced by surgery in cancer and non-cancer patients

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Cytokines have a vital and integral role in cellular and humoral immunity. They are produced by different types of cells following endogenous or exogenous stimuli such as tumour, infection and trauma. The differences between immunological responses in patients with malignancies and those with benign diseases undergoing surgery were evaluated in a prospective study.

Blood levels of interferon- γ (IFN- γ), tumour necrosis factor α (TNF- α), interleukin 1 α (IL-1 α), interleukin 1 β (IL-1 β) and interleukin 2 (IL-2) were determined in ten patients with intra-abdominal carcinomas (group A) and in ten patients with benign diseases (group B) before and during surgery (in the middle of the surgical procedure and by the time of skin closure) and on the first and seventh postoperative day. The anaesthesia regimen, the trauma induced by surgery and the blood loss were similar without postoperative complication. Heparinized blood (0.6 ml) was incubated with phytohaemagglutinin (7.5 μ g ml⁻¹) at 37°C. TNF- α was determined after an incubation time of 24 h. IFN- γ , IL-1 α , IL-1 β and IL-2 after 96 h of incubation using the enzyme-linked immunosorbent assay.

The preoperative IFN- γ level was 18 ng ml⁻¹ and decreased significantly to an intraoperative value of 5 ng ml⁻¹ (median) and remained at this level in both groups after operating. TNF- α , which had a median preoperative level of 1.1 ng ml⁻¹, decreased significantly during the surgical procedure but increased after surgery. At the seventh postoperative day it reached the preoperative value without showing any difference between both groups. IL-1 α levels showed no changes (preoperative median 130 pg ml⁻¹). IL-1 β was constant in group B whereas it decreased continuously in group A (preoperative median 3 ng ml⁻¹, postoperative median 0.5 ng ml⁻¹ at day 7). IL-2 decreased from a preoperative value of 1.7 ng ml⁻¹ to a level of 0.75 ng ml⁻¹ in both groups.

The results suggest that surgery suppresses the immunological status in patients with and without malignancy. Furthermore, the immunological response of cancer patients after surgery was suppressed. The occurrence of postoperative complications in cancer patients could be due to this reduced immunological status.

Surgical treatment of intra-abdominal multivisceral metastasis and intra-abdominal tumour recurrence

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From 1988 to 1990 593 patients underwent surgery for intra-abdominal malignancies; 358 patients underwent 552 operations because of intra-abdominal metastasis or tumour recurrence.

These 552 operations were analysed. There were 64 procedures for tumour recurrence (17 patients had one operation, 16 had two operations, one had three operations, two had six operations); 50 procedures for metastasis (34 had one operation, eight had two operations); and 438 procedures for primary metastasizing tumours (117 had one operation, 144 had two operations, 15 had three operations, four had four or more operations).

Radical (188 of 552; 34 per cent) and local radical (109 of 552; 20 per cent) procedures were predominant, while tumour reduction was carried out in 85 cases (15 per cent) and palliative operation in 134 cases (24 per cent). In radically and palliatively treated patients adjuvant chemotherapy followed in 49 patients.

Nearly half (249; 45 per cent) of the operations were performed in cases of emergency, especially for obstructive ileus or intra-abdominal perforations.

In emergency cases of intra-abdominal tumour recurrence and metastasis, radical tumour surgery has to be the aim. In 82 per cent of these patients the life-threatening situation could be controlled and 71 per cent left hospital with satisfactory life quality. The combination of repeat surgery with adjuvant therapy seems to be superior to chemotherapy and/or radiotherapy only. Repeated surgical intervention can control malignant disease over many years with good quality of life.

Advanced gynaecological cancer and recurrence: results of a prospective study with comparison of clinical imaging and pathological staging

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Between January 1988 and April 1991, 57 patients with advanced gynaecological cancer underwent investigation before operation by gynaecological examination and endosonography (ESG) under general anaesthesia: abdominopelvic computed tomography (CT) was performed in 49 patients and magnetic resonance imaging (MRI) in 21. There were 34 primary tumours and 23 cases of recurrence. Tumour types were: 38 cervical cancers (26 primary and 12 recurrences), eight ovarian cancers (four primary and four recurrences), three recurrences of endometrial cancer, five uterine sarcomas (one primary and four recurrences) and three primary vaginal cancers. All patients underwent laparotomy.

This prospective study compares the data from clinical and imaging examinations with results obtained from histological examination of surgical resection specimens. Depending on the presence of anterior or posterior tumour extension, the accuracy of clinical evaluation and preoperative imaging were studied for invasion of the posterior vesical wall and the vesicovaginal septum or of the anterior rectal wall and the rectovaginal septum.

Histological examination revealed vesical involvement in 17 patients and vesicovaginal septum involvement in 21. The accuracy of clinical examination, ESG, cytосcopy, CT and MRI was 83, 88, 87, 75 and 81 per cent, respectively, for vesical extension. Cytосcopy was not taken into account for evaluation of extension to the vesicovaginal septum; accuracy was 80, 90, 67 and 86 per cent for clinical examination, ESG, CT and MRI, respectively. Histological examination showed rectal involvement in 14 patients and rectovaginal septum involvement in 19. The accuracy of clinical examination, ESG, CT and MRI were, respectively, 91, 98, 89 and 71 per cent for extension to the anterior rectal wall. For extension to the rectovaginal septum, accuracy was 80, 96, 75 and 57 per cent for clinical examination, ESG, CT and MRI, respectively.

Endosonography would appear to be a useful addition to examinations for local extension of advanced gynaecological cancers. Its accuracy is superior to that of other examinations. As it is performed under general anaesthesia, there is no discomfort for the patient during this low-cost procedure.

Review of 77 pelvic exenterations for gynaecological malignancies

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Seventy-seven patients underwent pelvic exenteration between January 1980 and February 1990 (31 anterior, 19 total, 21 posterior, six atypical procedures). The mean age was 51.6 (range 32–81) years. Fifty-eight exenterations (75 per cent) were for carcinoma of the cervix: 28 for recurrence after surgery and/or radiation, and 30 for primary stage IV. Nineteen were for other malignancies: endometrium, five; ovarian, six; sarcoma, four; vagina, three; vulva, one. In all, 40 were considered retrospectively to be curative, and 37 to be palliative because of bilateral pelvic or aortic nodal metastasis, pelvic peritoneal floor involvement, or pelvic wall involvement. Seven of the 77 patients were operated on again and underwent total exenteration for recurrence after primary anterior or posterior exenterative operation.

The mortality and morbidity rates were calculated on 77 pelvic exenterations. Inpatient mortality rate was 12 per cent (nine of 77) at 90 days. Sixty-seven complications occurred in 43 of 77 exenterations before discharge, the morbidity rate was 40 per cent after anterior and atypical exenteration and 70 per cent after posterior and total exenteration ($P < 0.01$); 18 patients (23 per cent) were reoperated on for immediate postoperative complications.

The overall actuarial survival rate for the entire group was 33, 27 and 15 per cent at 2, 3 and 5 years (postoperative mortality included). Survival was 52 per cent at 3 years and 29 per cent at 5 years after curative exenteration (*versus* 7 per cent at 2 years after palliative procedures, $P < 0.001$). The survival rate was improved after anterior and atypical exenteration; 45 per cent at 3 years and 36 per cent at 5 years (*versus* 4 per cent at 3 years after posterior and total exenteration, $P < 0.001$).

Krukenberg tumour: factors influencing prognosis

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The Krukenberg tumour is a rare ovarian neoplasm which is usually secondary to a gastrointestinal malignancy. A retrospective study of the pathology records of a UK region for the period 1970–1984 identified 15 ovarian tumours that fulfilled the criteria for the diagnosis of Krukenberg tumour.

The incidence was 0.16 per 100 000 women per annum. At presentation ten patients were in their fourth or fifth decades; nine were premenopausal. Abdominal pain (ten patients), abdominal swelling (seven) and general symptoms of malignancy (11) were the most common presenting features; eight patients had a pelvic mass. At laparotomy nine patients had bilateral tumours and nine had ascites. The primary site was identified in ten patients.

Patients with unilateral tumours survived a mean of 10 months longer than those with both ovaries involved. The mean survival time of patients with ascites at presentation was 15.5 months; absence of ascites improved survival to a mean of 30 months. Patients with primary tumours diagnosed before or at the time of the discovery of

their Krukenberg tumour survived for a mean of 37.1 months. The mean survival time of those whose primaries were discovered after the Krukenberg tumour was 5.3 months; if the primary site remained unknown, mean survival was 6 months. Identification of the primary tumour after removal of the ovaries does not improve the prognosis of patients with this condition.

Retroperitoneal lymph node dissection after chemotherapy for advanced testicular cancer with preservation of sexual function

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Fifty patients (mean (range) age 27 (17–53) years) were subjected to retroperitoneal lymphadenectomy after chemotherapy for disseminated non-seminomatous germ cell testicular cancer.

Removal of the retroperitoneal mass was complete in 39 patients (78 per cent). In these, fibronectin tissue only was found in 17 and mature teratoma in 14. Of these 31 men, 30 are alive and well; one died with disseminated disease. In the 11 patients (22 per cent) where removal was incomplete, one with mature teratoma and three with fibronectin tissue are alive and well. Six of the seven with active cancer are dead.

In the 16 cases where it was possible to preserve one sympathetic chain, ejaculation was normal by 3 months after surgery in nine patients (56 per cent). In two further cases, normal sexual function returned after 9 and 21 months.

This series suggests that radical salvage lymphadenectomy may sometimes be performed with a good therapeutic result without loss of ejaculation.

Primary extranodal lymphoma of the gastrointestinal tract: a surgical approach

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The gastrointestinal tract is the predominant site of extranodal non-Hodgkin's lymphoma. In order to evaluate the role of surgery in diagnosis and treatment as part of a multimodal approach to therapy, a retrospective study with a 5-year follow-up was performed.

Between January 1986 and March 1990, 457 patients with malignant lymphoma underwent treatment at this hospital. In 38 patients a primary manifestation was detectable; 33 underwent surgical treatment. Consecutive chemotherapy and/or radiotherapy was performed in 23 cases. During the average follow-up of 47.8 months six patients died.

Results show that prognosis was dependent on tumour stage, radicality of the operation, tumour size and splenic infiltration.

Interstitial photodynamic therapy of rat liver metastases

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Photodynamic therapy (PDT) with dihaematoporphyrin ether/ester (DHE) as a photosensitizer has been used successfully in the treatment of various malignant tumours. The application in liver tumours has been restricted owing to the preferential retention of DHE in this organ. The limited light penetration during superficial irradiation prevents treatment of deeper-seated or larger tumours. We therefore investigated the effects of PDT using interstitial irradiation in a rat liver metastasis. A piece of 2 mm³ syngeneic colon carcinoma CC531 was implanted in the liver of 108 Wag/Rij rats. Tumours were treated on day 20 after implantation when their diameter was about 6 mm. In groups of six animals each the tumours were irradiated interstitially 48 h after intravenous administration of DHE 5 mg kg⁻¹, with 625 nm light at 50 mW cm⁻¹ and either 100, 200, 400, 800 or 1600 J cm⁻¹. Three control groups received either laser irradiation only, DHE only or diffuser insertion only. Short-term effects were studied by light microscopy in animals killed on the second day after treatment. The areas of liver and tumour necrosis and the area of vital tumour tissue were measured using a

computer-assisted integration of the circumference. Long-term effects on tumour remission were evaluated in animals killed on day 36. To determine liver damage, serum alanine aminotransferase and aspartate aminotransferase levels were measured on days 1 and 2 after treatment.

Tumour necrosis was found to increase with light dose, but nests of vital tumour tissue were still present in most of the cases. At 100 J cm^{-1} necrosis was 66 per cent of the total tumour area compared with 99 per cent at 1600 J cm^{-1} . The rim of surrounding liver necrosis also increased with light dose delivered, which could be confirmed by serum concentration of liver enzymes. Best long-term results were obtained at 800 J cm^{-1} , with complete tumour remission in four of six animals.

The results of this study show the ability of interstitial PDT to cause major destruction of solid tumour tissue in the liver combined with acceptable accompanying liver necrosis.

Duodenogastric reflux and gastric cancer in the rat

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Long-term duodenogastric reflux has been implicated in the genesis of gastric stump carcinoma after previous partial gastrectomy for benign disease.

The aim of this experimental study was to assess the effect of permanent biliary (BR), pancreatic (PR), and biliopancreatic reflux (BPR) on gastric mucosa. A gastric suture group was used as a control.

After 2 months' exposure, gastric mucosa displayed no macroscopic changes regardless of the type of reflux. On histological examination no intestinal metaplasia, hyperplasia or dysplasia was found. The only lesion found was the presence of numerous intramucosal cysts near to the anastomosis. The mean number of intramucosal cysts was 119 for BR ($n = 5$), 106 for PR ($n = 6$), 60 for BPR ($n = 5$) and 13 for the control group (gastric suture, $n = 5$).

The effect of long-term exposure (1 year) was investigated in the BPR group ($n = 9$). Macroscopic examination showed a protruded lesion on the anastomosis of eight rats. On histological examination these tumours were in six cases an adenocarcinoma and in two cases a benign submucosal adenocystic proliferation. The six adenocarcinomas occurred in five cases on an adenocystic proliferation, and in one case on an inflammatory granuloma.

These results show a clear correlation between long-term exposure of BPR and gastric carcinoma in rats. Histological investigation suggests that carcinoma arises through adenocystic proliferation, a condition similar to human gastritis cystic polyposa, generally considered to be a premalignant condition. This experimental model might prove useful for further investigation.

Stress and immunity in cancer patients undergoing surgery

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Stress may affect the immunological response in rodents and humans. The aim of this study was to ascertain the relationship between (a) plasma cortisol levels, nocturnal fall of plasma cortisol (NFPC) and urine excretion of catecholamines (UEC), and (b) lymphocyte population percentages in peripheral blood and *in vitro* cellular response to mitogens in cancer patients undergoing surgery.

A total of 16 patients with breast cancer and 22 with digestive tract cancer (age range 28–86 years) was studied. At 08.00 and 20.00 hours of the day before surgery the plasma cortisol levels were measured by radioimmunoassay. CD3 (T), CD20 (B), CD4 (T helper), CD8 (Ts-c) and CD16 (natural killer) cell percentages in peripheral blood were measured at 08.00 hours on the day of surgery by means of flow cytometry using monoclonal antibodies. Lymphocyte transformation tests (LTT) to phytohaemagglutinin and concanavalin A were performed by means of standard methods. UEC was measured by chromatography on the day before surgery. Patients showed mean (s.d.) CD3 and CD8 levels below the normal range (62(7) and 17(4)) and depressed LTT. In all, 21 patients (55 per cent) showed a NFPC level under the normal value. An inverse linear correlation between ECF and CD4/CD8 index ($r = 0.35$, $P < 0.05$) and a direct linear correlation between urine excretion of metapinephrine and CD4 ($r = 0.31$, $P < 0.05$) were found. In addition, NFPC below the normal value was associated with a CD8

level below the normal range in peripheral blood ($\chi^2 = 4.8$, $P < 0.05$). A correlation between LTT and stress variables has not been found.

In conclusion, peripheral blood percentages of immunocompetent cells below the normal range before surgery show an association with altered serum cortisol levels in patients undergoing surgery for cancer.

Faecal occult blood screening for gastrointestinal symptoms

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The place of faecal occult blood testing to indicate the urgency of investigation in patients referred with lower gastrointestinal symptoms has been evaluated. All patients with lower abdominal pain or altered bowel habit were posted a Haemoccult kit and asked to return three faecal specimens before surgical consultation.

In 518 patients the compliance rate was 88.4 per cent and the minimum follow-up was 15 months. There were 51 positive results from 458 tests (11.1 per cent) of which 19 were false positive (specificity 95 per cent). There were 23 patients with colonic cancer, 22 with adenomatous polyps and 26 with inflammatory bowel disease. There were 39 false-negative tests in patients with colonic disease (sensitivity 45 per cent) but within this group the sensitivity for adenomatous polyps was two of 22 (9 per cent), for inflammatory bowel disease 11 of 26 (42 per cent), and for colonic cancer 19 of 23 (83 per cent). Of the four colonic cancers with false-negative tests, one was caecal and three were rectal.

The Haemoccult test is sensitive for colonic cancer although fresh blood from rectal tumours may be missed. There were few false-positive tests but in this study the sensitivity for colonic polyps was very low. The Haemoccult test may serve as a guide to the urgency of investigation but it is not an adequate test for colonic pathology.

Non-endocrine cervical tumours: management and surgical treatment

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A cervical mass is a pathology frequently encountered in general surgery. A complete clinical history should be compiled to include age, tumour characteristics and associated lesions. Diagnosis is completed using complementary examinations: analysis, simple and contrast radiographic techniques, ultrasonography, computed tomography, endoscopy, ear, nose and throat examination, and fine needle aspiration and biopsy.

Problems arise in malignant secondary adenopathies in which the original tumour is unknown. Eighty per cent originate in the respiratory and upper digestive systems, although results of the biopsy should be taken into account before further study. Once diagnosis is confirmed, treatment should be surgical unless complications exist. Radiotherapy is used in association with surgery.

From 1985 to 1990, 135 patients (83 men, 52 women) with a mean age of 41 years underwent surgery. There were 93 localized benign processes, five acute adenopathies, eight chronic adenopathies and 29 carcinomas, of which 25 were metastatic. The surgical techniques most often used in cases of benign pathology were removal of the tumour (60) and draining of abscesses (44). Radical dissection (14) was the technique most widely used for neoplasias, while broadened dissection was employed in four cases. Morbidity rate was slight (8.1 per cent) and mortality nil. Mean admission time was 11 days.

Digestive free flaps for reconstruction in the head and neck

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Reconstruction with digestive free flaps (upper digestive tract only) has become a well established technique.

We have operated on 305 patients with a digestive free flap for head and neck reconstruction with microsurgery: 145 jejunal free flaps for hypopharyngeal cancer, 103 omental or gastro-omental free flaps, 46 forearm free flaps, eight fibula free flaps for mandibular reconstruction and three latissimus dorsi free flaps for mouth

reconstruction. A saphenous vein bypass was necessary in 11 cases for revascularization.

Two deaths occurred during the first postoperative month due to infections. The failure of the free flaps depended on the type of flap utilized: six failures occurred in 145 jejunal free flaps; no failures occurred among the forearm, fibula and latissimus dorsi free flaps.

Fifteen fistulae and six strictures were observed with free flaps used for reconstruction of the hypopharynx. Monitoring of these free flaps was performed by clinical, endoscopic and Doppler examination.

In conclusion, the low morbidity rate and the good functional and aesthetic results obtained in this series are convincing arguments for using these procedures.

Effect of adjuvant treatment on nutritional status and outcome in oesophageal carcinoma

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The effect of combination therapy (chemotherapy and radiotherapy) on nutritional status and outcome was studied in 47 consecutive patients with oesophageal carcinoma. Patients aged 76 years or less without metastases were randomized to receive chemotherapy (5-fluorouracil and cisplatin), radiotherapy (40 Gy) and surgery, or surgery alone, while patients over 76 years were treated by surgery. All patients were assessed nutritionally and parameters of weight loss (percentage fat reserve, body-mass index (BMI), serum albumin) recorded.

Weight loss (%)	Chemotherapy, radiotherapy and surgery (n = 19)	Surgery (n = 28)
< 10	10	13
10-20	6	11
>20	3	4

The mean BMI for the adjuvant group was 22.4 per cent and for the surgery group 22.5 per cent (*P* not significant). There was no difference in percentage fat reserve between the groups. The postoperative mortality rates for the combination therapy group were 16 per cent and in the surgery group 7 per cent (*P* not significant). Seven patients in the adjuvant group gained weight following treatment while 12 lost weight. No complications occurred in the weight-gain patients while all three deaths occurred in the weight-loss group. At follow-up 14 patients in each group were recurrence-free 2-10 months after operation. Six deaths occurred in the surgery group and two in the adjuvant group at follow-up. While nutritional assessments did not predict individual outcome, these results suggest a trend towards improved survival in the adjuvant group. This must be balanced against potential perioperative mortality in malnourished patients.

Risk of venous thromboembolism in oesophageal cancer surgery

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Deep vein thrombosis (DVT) is a common, serious but preventable complication of major surgery. The objectives of this study were: (1) to estimate the risk of DVT in patients with squamous cell carcinoma of the oesophagus (SCCO); and (2) to evaluate the incidence of DVT and embolism after oesophageal resection for cancer.

A DVT risk factor index was calculated prospectively for 53 consecutive patients with SCCO using the formula:

$$I = -8.08 + 0.185a + 0.008b - 2.24c + 2.02d - 0.054e - 0.118f - 0.006g$$

where *a* is age (years), *b* is euglobulin lysis time (min), *c* is previous abdominal surgery (yes = 1, no = 0), *d* is varicose veins (present = 1, absent = 0), *e* is antithrombin III (per cent), *f* is cigarettes smoked per day and *g* is platelet count ($\times 10^9 \text{ ml}^{-1}$). Patients with large

positive scores were most likely and those with large negative scores least likely to have DVT after operation. Ninety-one per cent of patients with DVT were correctly predicted when a cut-off point of -1 was used. In addition, data regarding postoperative DVT and pulmonary embolism were analysed retrospectively for 127 patients who underwent oesophagectomy for SCCO (without anticoagulant prophylaxis). The diagnosis of DVT and/or thromboembolism was based on clinical grounds, ultrasonography and/or autopsy.

The mean(s.d.) value of DVT risk factor index was found to be -4.4(3.5). Only four SCCO patients had a positive index, while in 45 patients (85 per cent) it was ≤ -1 . Among patients who underwent resection, one developed DVT and one died owing to pulmonary thromboembolism.

Prophylactic measures significantly reduce the frequency of postoperative DVT and embolism but may increase the frequency of haemorrhagic complications. Our findings demonstrate that the vast majority of patients with SCCO are at low risk of developing postoperative DVT embolism. The frequency of clinically established DVT/embolism after oesophageal resection was low in this series also. In our opinion, therefore, routine anticoagulant thromboprophylaxis in oesophageal cancer surgery is not justified, and may well be dangerous for those who undergo blunt oesophageal resection. Anticoagulant prophylaxis may be withheld only in a small subset of carefully identified high-risk patients, but in these patients blunt resection is not recommended.

Functional evaluation of proximal femur prostheses implanted for tumour surgery

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Between 1987 and 1991, 20 prostheses for proximal femur replacement were implanted in 19 patients (ten men and nine women) of median age 60 (range 15-89) years.

Four prostheses were implanted for a primary tumour (MFH, osteosarcoma, Ewing's sarcoma, liposarcoma), ten for metastatic disease secondary to breast neoplasia, three for pulmonary neoplasia, three for prostatic neoplasia and one for a renal carcinoma. Of the 16 patients with metastatic lesions, 12 presented with a pathological fracture. Other surgical indications were uncontrolled pain, inability to walk and considerable bone lysis with danger of fracture.

The femoral head, neck and trochanters were always resected. The smallest resection was of 7 cm and the largest 26 cm. We used a bicentric cup and all prostheses were cemented in place. Walking with partial weight-bearing was started 7 days after surgery.

Follow-up was impossible for five patients (six prostheses) because of rapidly progressive disease (two), fatal myocardial infarction (one) and fatal lung disease (two). There was no luxation, no postoperative infection and no implant failure. One case of deep vein thrombosis was encountered. Pain and function were classified according to the SICOT system.

Pain was controlled in all cases except one, who presented with a massive pulmonary metastasis. After surgery, all patients could walk without help. Physical examination revealed weakness of abduction, a Trendelenburg sign and limping. All patients except one were able to enjoy lengthy walks.

This procedure has several advantages. It reduces the risk of local recurrence because all the tumour region is resected (unlike other systems where late dislocations of the implant are often observed), and it gives good control of pain and good functional results that increase the quality of life of terminal cancer patients.

Surgical treatment of retroperitoneal tumours between 1978 and 1991

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Retroperitoneal tumours are rare and histologically there are numerous varieties. Our management of these tumours has been reviewed to delineate their natural history and to assess the effect of surgical resection and administration of additional therapy.

This report includes 53 patients seen in a period of 14 years (1978-1991) with retroperitoneal tumours, 70 per cent of which were malignant. The mean age of the patients was 41.7 (range 2-77) years

and the mean duration of symptoms was 7.6 months. Most patients presented with a palpable mass (62 per cent) and pain (50 per cent). Liposarcomas were the most common malignant tumours (23 per cent), schwannomas were the most common benign tumours (40 per cent).

Tumour node metastasis (TNM) classification of the retroperitoneal sarcomas revealed T₂ in 26 per cent and T₃ in 74 per cent of cases. The histological grade was G₁ in 33 per cent, G₂ in 11 per cent and G₃ in 56 per cent; 3 per cent were M₁.

The main factor in determining resectability was the extent of retroperitoneal fixation and adherence to vital structures rather than the size of the tumour. In benign tumours, total excision was performed, but in sarcomas complete resection with tumour-free margins was performed in 55 per cent of cases with partial resection in 29 per cent. Biopsy only was performed in 16 per cent. The adjuvant postoperative treatment varied considerably and was administered in 40 per cent of patients. In 27 patients with sarcomas, 37 operations were performed either to excise the tumour completely or for a 'second look'. Adjacent organ resection was required to avoid leaving gross tumour in 15 per cent of these operations. The organ most frequently resected was the kidney (11 per cent). Operative mortality was 4 per cent.

The surgical management of patients with retroperitoneal tumours requires every effort for complete resection of the tumour with an adequate margin of normal tissue to improve long-term survival. Our results show that extensive surgery can be performed with a low mortality rate even in advanced cases.

Surgical management of primary retroperitoneal liposarcoma

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This study analyses six cases of retroperitoneal liposarcoma (four men and two women, aged 55–75 years), undergoing operation in this department during the period 1970–1990. All patients underwent operation with the primary diagnosis of a retroperitoneal tumour. The main symptoms and clinical findings were a palpable abdominal mass in five patients, abdominal pain in four, fever in two, weight loss in two and constipation in two. The main diagnostic methods until 1980 were radiography of chest and abdomen, intravenous pyelography, radiographic examination of the gastrointestinal tract, and, since 1980, computed tomography and ultrasonography. In all six

patients the tumour was extirpated, despite its mean weight (6 kg), and in two patients nephrectomy was performed simultaneously. Seven operations were performed as one patient had to undergo surgery again within a year owing to a recurrence. After operation, four patients continued treatment with radiotherapy. One patient, who subsequently received chemotherapy, is alive 14 months later; one patient died in the intensive care unit from cardiorespiratory failure on the first postoperative day; one patient died 1.5 years later from cardiorespiratory failure; the other three patients died 1.5–2 years after operation. The study concludes that, despite the progress of radiotherapy and chemotherapy, the prognosis of retroperitoneal liposarcoma continues to be poor. The treatment of choice in most cases must be the extirpation of the tumour. Moreover, even when surgery is radical, postoperative (and, in some cases, preoperative) radiotherapy is indicated.

Major device-related complications during locoregional chemotherapy

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The use of totally implantable systems for locoregional chemotherapy is associated with complications due to both drug toxicity and the management and nursing of the system. The latter is important because in most cases the complication results in suspension of treatment. The aim of this study was to report experience with the implantation of systems for locoregional chemotherapy in 37 cases for hepatic arterial chemotherapy and in 14 cases for intraperitoneal chemotherapy. Fully implantable systems were used in all patients with the catheter inserted in the hepatic artery via the gastroduodenal artery. A Tenckhoff-type system was used in all patients for intraperitoneal chemotherapy. Five major complications were observed in the first group (14 per cent): two dislodgements of the catheter in the duodenal lumen, two occlusions (one associated with hepatic artery thrombosis), and one rupture of the catheter. In the second group only one complication (7 per cent) was observed: dislodgement of the catheter into the small bowel lumen. In all cases chemotherapy was interrupted. Based on their experience and literature review, the authors analyse possible causal factors and report suggestions to reduce the incidence of major complications.

Isolated fracture of the ulna and its early functional treatment

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Isolated fractures of the ulna are problematic. Healing is prolonged and often ends in pseudarthrosis.

In recent years there have been many changes in management – more fractures are operated on, or if treated conservatively, long-arm plasters are used to avoid movement of the fragments.

Since 1984, in this department, these fractures have been treated neither by operation nor by immobilization. A total of 34 fractures has been treated only by an elastic bandage or initially by a short arm plastercast or brace for not more than 10 days.

Mobilization after this was tolerated by all patients. We have seen only good functional results with free joint movement, especially free rotation movement of the forearm. After 6 weeks all patients were fully reintegrated in work or private life, without any loss of function. Radiographic control showed stable bone callus.

An additional study on cadavers was also undertaken.

External fixation of displaced fractures of the proximal humerus

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Since Neer published his classic study of fractures of the proximal humerus, in which he described methods of classification and an assessment of the results of treatment, there has been disagreement on the management of severe displacement. For badly comminuted fractures which involve the articular surface, either total or partial joint replacement seems to be the treatment of choice.

There is no consensus on the treatment of displaced two-, three- and four-part fractures. There is a range of treatment methods: closed, open reduction and internal fixation, and arthroplasty. This relative failure of established methods indicates that alternative techniques should be evaluated. A technique for transcuteaneous reduction and external fixation of displaced fractures of the proximal humerus is presented with special emphasis on technical errors and complications related to the fixator. Between January 1989 and January 1991 ten proximal humeral fractures were treated by closed reduction and external fixation with the Hoffman type of fixator.

With the patient under general anaesthesia, and in a supine position, a Steinmann pin was introduced transcuteaneously into the major head fragment under image intensifier control and used to help reduce the fracture. This reduction was maintained by an assistant, while two half-pins with continuous threads were drilled into the humeral head and two or three pins into the humeral shaft. A neutralizing bar was applied and the Steinmann pin removed. In one patient there was a pintract infection. The early functional results were assessed according to the Neer numerical score system. Four cases were excellent, five satisfactory and one unsatisfactory.

In conclusion, satisfactory fracture reduction and stability, a low rate of complication and good early functional results have been obtained by transcuteaneous reduction and external fixation. It is a useful alternative in the treatment of displaced fractures of the proximal humerus.

Formation and prevention of habitual shoulder dislocation

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In a retrospective study of 177 cases of shoulder joint dislocation in the years 1974–1981 it was found that in 9 per cent there was 'false' habitual dislocation because there had been a new traumatic event sufficient to explain the dislocation. Nuclear magnetic resonance diagnosis and arthroscopy can reduce the rate of habitual shoulder dislocation. The duration of immobilization of the shoulder articulation is an important factor in the prevention of relapse.

Glenoid fractures, large lip ruptures of the glenoid and Hill–Sachs lesions require surgical treatment. It is important to explain the severity and possible complications to the patient. The diagnosis and the modern use of shoulder arthroscopy can optimize therapy and reduce the frequency of habitual shoulder dislocation.

Arthroscopic fixation of osteochondral fragments with biodegradable material

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Since Ambrose Paré described osteochondral fragments in the knee, discussion about the optimum treatment has continued. One solution is to fix the fragment.

The aim of this study was to develop a technique and instruments to fix the fragment arthroscopically with biodegradable pins. This combines the advantages of arthroscopic procedures – less morbidity and discomfort, shorter hospital stay and far better cosmetic results – with the advantage of the one-stage operation, because of the spontaneous degradation of the osteosynthesis material.

Five patients were treated in this way, four with a fragment secondary to osteochondritis dissecans and one with a fresh osteochondral fracture. All lesions were located on the weight-bearing part of the femoral condyle.

All lesions healed, though in one patient a refracture occurred after 4 months. Subsequently she was treated with a perichondrium transplantation and has been well since. In another patient, the osteosynthesis pin was reinforced with two small fragment screws 6 weeks later, arthroscopically, to give more compression.

The outcome seems to be encouraging and further studies will be undertaken.

Expression of extracellular structural proteins and vasculature in arthroscopic biopsies of cruciate ligaments

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The present study was undertaken to determine the microstructural and histochemical properties of the anterior (ACL) and posterior (PCL) cruciate ligaments of the human knee under normal and diseased conditions.

Specimens of cruciate ligaments from patients with rheumatoid arthritis (RA, $n = 10$) and osteoarthritis (OA, $n = 9$) were taken during knee joint arthroscopy. The binding patterns of neoglycoproteins, lectins and matrix monoclonal antibodies were examined by use of light microscopy and transmission electron microscopy. Normal human tissue ($n = 8$) served as a control group.

In normal ligaments the fibrillary matrix contained small oxytalan fibres. In PCL the collagen fibrils were arranged in dense parallel bundles. In ACL the fibrils also showed a circular and vertical organization. The binding pattern of tenascin and fibronectin showed no difference between the ligaments. The matrix of ACL contained more β -galactose and N -acetyl- β -galactose molecules. In PCL significantly more vessels were seen. In OA both ligaments showed disorientated collagen type I fibrils and a loss of banding patterns. Wheat germ agglutinin revealed a higher affinity to the extracellular ground substance compared with normal tissue. In areas of severe destruction acid mucopolysaccharides were enhanced. In RA, in inflamed areas of both ligaments sialic acid molecules were diminished and sulphated proteoglycans were focally accumulated. Endogenous lectins binding mannose, sialic acid and fucose were enhanced. Focal fibrin aggregates and the binding pattern of *Phaseolus vulgaris* agglutinin E and peanut and *Ricinus communis* agglutinins correlated with the endoscopic findings of hyperaemia and oedema. In ACL alone the arrangement between the fibrils was disturbed and dysplastic filaments were found. In these ligaments type III collagen and fibronectin were enhanced, whereas type VI collagen remained intact. Vasculature was significantly enhanced. This finding was correlated with an enhanced expression of tenascin and laminin. Demonstration of Gal- β (1-3)GalNAc was confined to areas with significant ultrastructural changes bordering the lumen. Alterations in matrix architecture were not restricted to areas near the inflammatory pannus. In PCL, the orientation and composition

of the fibre systems were not significantly altered. The number of its vessels was not significantly increased.

RA induces complex alterations of proteoglycan and protein components. In contrast to OA, rheumatoid destruction of collagenous fibres showed a typical topographical pattern with significant changes in ACL. In contrast, PCLs were compact and well conserved. Perhaps the greater inflammatory process on the surface of ACL is responsible for the observed differences.

Short-term fasting does not affect skeletal muscle strength

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The effect of short-term fasting on maximal inspiratory effort, $P_{i(max)}$, and on dominant hand grip strength (Vigormeter) was tested in 64 healthy young adults. The volunteers were randomized into one of four groups ($n = 16$) with 0, 400, 800 and unlimited calorie intake for 24 h. Measurements were carried out at 0, 24 and 48 h.

Diet (calories)	Vigormeter (kPa)			$P_{i(max)}$ (mmHg)		
	0h	24h	48h	0h	24h	48h
0	119	112	119	105	93	104
400	116	114	120	103	100	105
800	114	118	118	103	102	101
Unlimited	117	120	124	105	102	102

The results showed no significant reduction in any of the groups at 24 h compared with the 0 h value. We conclude that in young healthy adults short-term fasting does not affect skeletal muscle strength.

Use of biocompatible orthopaedic polymers in the treatment of giant osseous cysts

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Twenty-five patients suffering from giant osteodystrophic fibrous osseous cysts and eight with osteoblastoclastoma underwent surgical treatment as follows. After bone cavities had been scraped out, they were filled with multiple thin chips (diameter 2–3 mm) of the biocompatible polymers vinylpyrrolidone and methylmethacrylate; these were reinforced by polyamide fibres, which stimulated the reparative process. The fragments were immobilized by an original mini external fixation apparatus or by a plaster of Paris bandage. Using this method, times to full consolidation were 50 per cent shorter on average than with the technique of bone resection and filling the defect with bone autograft.

Statistical analysis for evaluating patellar height changes following wedge osteotomy

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Postoperative patellar height changes were evaluated to optimize surgical decision-making in the preoperative phase. The aim was to predict the postoperative patellar height after wedge introduction and the critical conditions with regard to possible low-riding patella.

Patellar height was measured according to the definition of Caton and Deschamps. Seventy-nine men and 61 women aged 18–88 years volunteered for the study. All patients had undergone tibial osteotomy between 1979 and 1989 by the same surgeon using one protocol involving the correction of varus deformity by wedge osteotomy. This study is based on preoperative and postoperative radiographic measurements following the protocol of Ramadier. The mean varus angle was 5.5° and the mean wedge length was 11 mm. Linear regression with two independent variables showed a significant correlation between wedge length and patellar height and postoperative results.

Based on a threshold ratio of 0.6 for patellar height, critical preoperative conditions for low-riding patella have been identified. The critical values are wedge length >17 mm and patellar height <0.7; an additional correction protocol must be planned to avoid low-riding patella.

Treatment and long-term results in 437 fractures of the proximal femur in the elderly

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A total of 437 patients with pertrochanteric and/or subtrochanteric fractures was treated with medullary nailing by the technique of Simon-Weidner, Ender. Only patients of 80 years and older were entered into the study. Of these 50.2 per cent had a pertrochanteric and subtrochanteric fracture with an isolated fragment of the minor trochanter. Lateral femoral neck fracture was present in 9.2 per cent. Three or four nails had been implanted in 88 per cent. After operation patients were allowed immediate remobilization with full weight-bearing.

Rotational immobility was found in 74 per cent of all cases and the complication of moving nails in 38 per cent. Mortality rate in hospital was 21 per cent with an average age of 84 years. Of the patients 118 were re-examined up to 24 months later at home. Of these patients 88.7 per cent were fully remobilized and without crutches. Two-thirds of these patients had no complaints of handicaps and accompanying morbidity.

We believe that stabilization with medullary nailing, in comparison with other operative techniques in the proximal femur, is the correct procedure for older patients.

Cruciate ligament replacement by polydioxanone-augmented grafts

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In order to reconstruct acute as well as long-established ruptured anterior cruciate ligaments, a standardized method of ligament transposition was used. A graft is formed from the medial third of the quadriceps and patellar tendon in which a suturing material of polydioxanone (PDS) is inserted. This graft is drawn through two drill holes from the medial part of the proximal tibia to the lateral femoral condyle where the anterior cruciate ligament is inserted, and fixed with two screws while the knee is in a 30° flexion.

Between 1 June 1988 and 31 May 1991 85 patients (63 men, 22 women; mean age 30 years) were operated on for a traumatically ruptured anterior cruciate ligament. In 40 patients the rupture of the anterior cruciate ligament was combined with other lesions of the ligaments of the knee. At follow-up examination, 68 patients classified the result as good or excellent.

We conclude that PDS-augmented graft replacement represents a good method in the treatment of ruptured ligaments of the knee. Besides a correct operation, postoperative physiotherapy is a precondition of a good long-term result.

Post-traumatic rupture of the extensor pollicis longus tendon

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Aetiology, interval between trauma and diagnosis, and the results of extensor indicis proprius transfer are discussed.

Between 1985 and early 1991 eight patients with a post-traumatic rupture of the extensor pollicis longus were operated on. Seven patients had wrist/hand trauma: five were diagnosed to have an undisplaced fracture of the distal radius, one had an undisplaced fracture of the scaphoid bone, one had blunt trauma to the thumb and in one patient the cause remained unknown. The mean age was 52 years. The length between trauma and time of diagnosis ranged from 1 to 28 weeks.

Seven patients were treated by transfer of the extensor indicis proprius and in one patient both ends were anastomosed. All patients were re-examined after operation except one who had died. The

strength in the operated thumb was reduced in four patients but did not result in discomfort in daily work. The same ratio was found in loss of active thumb flexion. Two patients were able to move the thumb above the plane of the hand. All patients had symmetrical extension. Six patients were satisfied with the final result and one had a nagging feeling at the end of the day.

Post-traumatic rupture of the extensor pollicis longus is rare. The undisplaced fracture of the distal radius is a possible predisposing factor, perhaps because of high pressure in the unruptured tendon sheath. In our opinion the transfer of the extensor indicis proprius is a good therapeutic option.

Detection of tenascin, fibronectin, and collagen types I, III, IV, V, VI, VII in rheumatoid tenosynovitis: new pathogenetic aspects of hand tendon ruptures in rheumatoid arthritis

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Tendon ruptures are a frequent problem in patients affected by rheumatoid arthritis (RA). The aim of the present study was to explain the insufficient function of hand tendons in RA.

Flexor ($n = 16$) and extensor ($n = 19$) tendon samples in RA were taken during surgical synovectomy and compared with a control group of normal tendons ($n = 31$). Samples were analysed by the combined use of morphometry, immunohistochemistry, scanning (SEM) and transmission (TEM) electron microscopy. Matrix proteins were detected with monoclonal antibodies.

In all rheumatoid tendons, the ultrastructural collagen architecture was markedly altered. Interfibrillary dysplastic fibrils (96 fibrils per square mm (fpsm)), fibrous long-spacing collagen (42 fpsm), and frayed fibrils (17 fpsm) were found. Fibril diameters in RA revealed a higher variability (range 20–490 nm; mean(s.d.) 98.6(48.8) nm) in comparison with normal hand tendons (range 20–290 nm; mean(s.d.) 118.3(34.7) nm). The average distance between the major bands in RA was reduced (from 57.3 nm down to 54.8 nm). Loose bodies with pathological 32-nm banding were detected in rheumatoid changed finger tendons. Oxytalan, elastin and mature elastic fibres were destroyed. No type VII collagen was expressed in normal tendons, whereas an intensive binding was noted for types I, III, IV, V and VI. In RA type IV and III collagens were dramatically increased. Type VI collagen was focally reduced. The immunostaining of fibrillar type I collagen revealed massive damage. In these areas no pannus was present. Tenascin was a major glycoprotein of the tendon matrix with strong affinity to fibronectin. During healing processes after rupture tenascin and fibronectin staining were markedly enhanced.

The findings suggest that a causal correlation exists between altered matrix substructure and insufficient function of tendon tissue in RA. Dysplastic collagen fibrils and critical damage of type I collagen are probably caused mainly by cytokines and not directly by pannus. Changes in collagen structure seem to be the decisive components for the development of tendon ruptures in RA.

Histological studies after *in vitro* laser irradiation of human articular cartilage and menisci in an attempt to define laser use in arthroscopic surgery

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To investigate the tissue reaction of human articular cartilage and menisci to local application of laser irradiation, articular cartilage and meniscal tissue harvested at surgery or autopsy were exposed to laser irradiation. For comparison an ultraviolet Excimer laser, an argon ion laser and a neodymium yttrium-aluminium-garnet (Nd:YAG) laser were used. Intensity, duration of exposure, frequency and interval times of irradiation were altered and recorded. Following special preparation techniques, the tissue was subjected to light microscope histological examination and to scanning electron microscope studies of the cartilage.

The use of so-called 'thermal lasers' (argon ion laser/Nd:YAG laser) caused greatest tissue damage as could be seen by a carbonization border zone and a much deeper coagulation necrosis as a result of the higher energy applied. In contrast, the use of the

Excimer laser resulted in marked tissue ablation with sporadic slight marginal tissue damage.

Using the light microscope, intact cell nuclei were seen up to the border of the cartilage ablation channel. Additionally, some surface sealing of cartilage tissue was possible by wrapping of the hyaline structures as seen after Excimer laser application.

In conclusion, *in vitro* experiments give no indication for the use of so-called 'thermal lasers' in arthroscopic surgery. In comparison, the Excimer laser, used under arthroscopic control, may have potential in arthroscopic joint surgery.

Cementless interlocking nailing of pathological long bone lesions: improved operative management

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The aim of this study was to evaluate the efficacy of locked intramedullary nailing with methylmethacrylate support, in pathological long bone destruction.

In the past decade, because of improved management of metastatic tumour and metastatic disorders, the frequency of long bone lesions requiring intervention has increased in conjunction with patient survival. The principles of management of such lesions are still developing and new operative techniques are evolving. Thus far, it is evident that rigid fixation of the involved bone allows early mobilization, reduces morbidity rates and prolongs patient survival.

Over a 3-year period 32 long bone destructive lesions in 24 patients required internal fixation in this unit. Five patients had more than one bone requiring surgery. The long bones involved were the femur in 27 cases and humerus in five. All patients were symptomatic and 14 of the procedures were performed before fracture occurrence. Intramedullary fixation was achieved by a variety of cross-locking devices including Russel-Taylor (19), Seidel (five), Gross and Kempf (three) and Zickel (five) intramedullary nails.

Pain relief was achieved in all cases. Approximately 90 per cent of the patients were ambulatory after surgery. No intraoperative deaths occurred but one patient died within 1 month of surgery from a myocardial infarction.

This experience would suggest that interlocking nail fixation without cement, allowing adequate load sharing, is a safe, effective technique in the management of pathological bone destruction.

Internal fixation of the hand

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A total of 1541 internal fixations of the hand is reviewed to evaluate conditions, complications and rules of treatment determining the outcome with respect to function.

During the review period 1061 primary and secondary internal fixations after acute hand injuries, 360 corrections of malposition, pseudarthrosis and functional defects of bone, and 120 elective reconstructions after complex hand injuries were studied for mechanism of injury, classification of trauma, choice of treatment, complications and results of movement.

The infection rate was 0.5 per cent for primary and secondary operations, below 0.5 per cent for elective osteosynthesis. In the past 4 years this department changed methods from internal fixation with K pins to A0 mini-implants, including 250 fractures and pseudarthroses of scaphoid bone, stabilized by internal screw fixation instead of Russe I or II technique. The osteosynthesis of the scaphoid allows reduction of immobilization by cast from 90 to 30 days.

Internal stabilization of hand fractures allows active mobilization immediately after treatment and reduces complications like Sudeck's atrophy and loss of movement. Overlooking the cases of the past decade this opinion could be verified.

Post-traumatic tear of the rotator interval

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The rotator interval is the triangular part of the shoulder capsule between the subscapularis and the supraspinatus. Different lesions of

the rotator interval have been described, mostly with anterior instability of the shoulder, but never a post-traumatic isolated tear.

This lesion was documented in eight cases, three women and five men, mean(s.d.) age 37(10) years with no previous shoulder pain. Five of them were athletes. All patients reported a paralyzing pain, after a direct or indirect injury, in internal rotation, and in one case after anterointernal subluxation. Two of them also noted a haematoma on the upper part of the anterior side of the arm. They recovered in a few days with rest and analgesia, but the pain recurred with activity.

Clinical examination showed no limitation in shoulder mobility, signs of subcoracoid impingement and symptoms of tendinitis of the long head of the biceps in all patients. There was no shoulder instability.

Radiographs were normal. Arthrography showed in all cases a large projection of the dye through the rotator interval tear, towards the subscapularis fossa. No rotator cuff tear, and no subluxation of the long head of the biceps tendon were visible on computed arthrography.

Six patients underwent surgery. Surgical exploration confirmed the rotator interval tear. The operative treatment consisted of acromioplasty, resection of the coracoacromial ligament and suturing of the rotator interval. The results were excellent.

This syndrome seems to be of interest to clinicians. The clinical features are characteristic. Arthrography confirms the diagnosis. Surgical treatment, based on suture of the rotator interval, gives excellent results.

Unreamed tibial nail, the logical choice

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The great advantage of intramedullary nailing of shaft fractures in the leg is the fact that this osteosynthesis can often bear weight at an early stage. Since the pioneering work of Küntscher in this field, there has been an intensive search for improvement in this technique. The original ideas of Küntscher were improved and further refined with the introduction of the interlocking nail. With this nail length, rotation of the bone can be easily controlled. However, reaming of the medullary canal is needed, which has a deleterious effect on the endosteal circulation of the cortical bone.

As the result of interlocking, jamming of the nail in the isthmus is superfluous; a thin nail will suffice. Introduction of a thin nail can be performed without reaming, so that the endosteal circulation is preserved. Moreover, a thin, solid nail lacks dead space, which may reduce the infection rate.

Recently, an 8-mm solid interlocking tibia nail that can be introduced by a closed procedure without reaming has been developed. This nail is used for closed and grade 1 open tibial fractures. The results of the first 20 treatments are presented. Early weight-bearing, the absence of infection and, to date, absence of pseudarthrosis, make it a promising method of treatment.

Combined gluteus medius–tensor fascia lata flap for coverage of trochanteric pressure sores

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A new musculocutaneous flap is described that is usable in trochanteric pressure sores in paraplegics. This reconstructive unit combines the muscular proximal segment of the tensor fascia lata (TFL) and gluteus medius muscles in a round flap pedicled on the lateral circumflex femoral artery. Anatomical dissections performed by us revealed an anastomotic network between the superior gluteal artery, which supplies the gluteus medius muscle, and the lateral circumflex femoral artery, the vascular supply of the TFL muscle.

Cutaneous defects of the trochanter and associated osteitis are frequent complications in paraplegic patients, often requiring osteotomy and coverage of bony prominences by well vascularized, padded skin. Musculocutaneous flaps are well suited for this purpose and we review various reconstructive units that may be used to cover trochanteric defects. Among these, the gluteus medius–tensor fascia lata flap appears as an excellent choice. In the case of recurrent ulcers, other donor areas are left intact and the flap itself could serve as a basis for a traditional TFL flap.

Primary arthroscopy in injuries and fractures of the ankle joint

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A total of 204 primary arthroscopies in injuries of the ankle joint has been performed in this department since 1990. After taking a history of the accident and clinical examination of the patient, a conventional radiograph and ultrasonographic examination were performed.

Indications for arthroscopy were haemarthrosis, to exclude associated injuries with osteochondral fractures, evidence of outer ligament rupture on video radiography, post-traumatic disorders, osteochondritic lesions, loose bodies, hypertrophic synovitis and radiological arthrosis.

Arthroscopy was performed under local or general anaesthesia using a 5-mm arthroscope with 30° telescope and usually without a distractor. The findings and surgical interventions were recorded on videotape. Haemarthrosis with different forms of outer ligament rupture was present in 89 per cent; 32 per cent showed additional osteochondral fractures and loosened flakes. Of this group 9 per cent underwent an arthroscopic procedure or arthrotomy.

Some cases of fracture of the lateral or medial malleolus were treated by transarthroscopic osteosynthesis. One case of long-term irritation of the superficial peroneal nerve was observed as a complication.

We conclude that the use of arthroscopy should be extended to the ankle joint and perhaps to other joints as well.

Experience with osteogenesis of bone transplants repopulated with the patient's own bone marrow cells

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Methods of producing faster integration of bone transplants into the host bone have been studied.

Experiments were performed on 25 rabbits whose hind legs underwent a transplant of boiled bone transplant or of deproteinized bone repopulated with their own bone marrow cells obtained by the puncture of the spongy bone of the same rabbit.

At 15, 30 and 60 days after operation, the operated leg was examined radiographically. Two days before the radiograph, that is, 13, 28 and 58 days after operation, six rabbits were given tetracycline to permit the study of the delimitation of the calcifying area. The animals were killed at 15, 30 and 60 days after operation, when macroscopic and microscopic examination of the resulting areas was performed, as well as fluoroscopy. Faster integration of these transplants than in controls was noted.

At 15 days after operation, invasion of the bone transplant and change into new bone tissue was noted, the Haversian canals being revascularized. After 30 days, revascularization of the bone transplant was total, the callus having a normal aspect. After 60 days the integration between the transplant and the host bone was good.

Following these good experimental results, four clinical cases were treated by congealed human transplants (phalanx) repopulated with the patient's own bone marrow cells, to reconstruct the bone structure of the mutilated hand. Deproteinized human transplant was used in 45 cases of carpal scaphoid pseudarthrosis, boiled human transplant was used in 31 cases and self-transplant was used in 12 cases, but in all cases the transplants were repopulated with the patient's own bone marrow cells. Good results were obtained in all these cases.

Use of a universal miniexternal fixation apparatus for fracture treatment

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In the Red Cross Hospital in Kaunas 72 patients with fractures of various long bones underwent closed osteosynthesis using a small external fixation apparatus of our construction. The fixator contains a screwed bar, rod holders and hard screwed rods. The holders may be easily fastened and moved in a proximal or distal direction. A light portable apparatus, weighing not more than 300g, ensured atraumatic reduction and high stability of fragments. A reliable immobilization allowed early weight bearing and walking (in 2–3 days after osteosynthesis), and promoted a better circulation, callus formation and consolidation.

Neonatal bile duct perforation and stricture

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Benign bile duct strictures are occasionally seen in early infancy. Usually, no cause can be identified and the stricture is said to be congenital. Spontaneous bile duct perforation is a rare entity which occurs in the first 12 weeks after birth. This disease may present as a subacute illness with jaundice, pale stools, failure to thrive and progressive biliary ascites. A pseudocyst may be found in the hepatoduodenal ligament at laparotomy. Both spontaneous perforation and stricture of the duct tend to be located just proximal to the junction of common bile duct and cystic duct.

We have analysed our patient data to assess whether infants treated for a neonatal bile stricture could have had a bile duct perforation before clinical presentation of the stricture. Three cases were found. Two had a Roux-en-Y hepaticojejunostomy for a bile duct stricture located at the junction of the common bile duct and the cystic duct at 3 and 20 months. One infant had a transient period of moderate jaundice associated with dilated intrahepatic ducts at 1 week. The other child had a period of melaena and haematemesis presumably caused by haemobilia 2 months after birth. In both cases the symptoms resolved spontaneously. The third infant underwent exploratory laparotomy for extrahepatic cholestasis 5 weeks after birth. A pseudocyst filled with bile was found in the hepatoduodenal ligament. The cyst was drained. The perforation site could not be identified. Two weeks after surgery, a biliary fluid collection was drained percutaneously. These cases suggest that spontaneous bile duct perforation may pass unobserved when located in the hepatoduodenal ligament, and may proceed to bile duct stricture.

Effect of birth weight on the clinical course of patients with neonatal necrotizing enterocolitis

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Neonatal necrotizing enterocolitis (NEC) is the most common surgical emergency in the newborn. Its incidence is rising owing to improved neonatal care and prolonged survival of premature infants.

We report 73 patients with NEC managed at the Children's Hospital, Oakland over a 5-year period. Twenty-six patients (39 per cent) were managed by operation with an in-hospital mortality rate of 7 per cent. Forty-seven non-operative patients (61 per cent) had an in-hospital mortality rate of 7 per cent. The average birth weight was 1395 g with 75 per cent less than 1500 g.

The mortality rates for patients weighing more than and less than 1500 g were not significantly different (5.2 versus 7.4 per cent). Mean age at diagnosis was 20.5 days for infants less than 1500 g weight at birth. Infants weighing more than 1500 g presented at an average of 8.6 days. Some 53 per cent of infants weighing more than 1500 g required operative intervention while 32 per cent of those weighing less than 1500 g required surgery.

These data suggest possible differences in the pathogenesis and clinical course of this disease for smaller and larger birth weight infants.

Value of hip radiography to screen for developmental displacement of the hip in breech-born infants

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The aim of this study was to assess the value of radiographic screening of breech-born infants in the first 6 months of life for developmental displacement of the hip.

During a 3-year period (1988–1990) there were 20 220 live births at our hospital. Of these, 571 were breech born (2.8 per cent), and 496 hips of breech infants were radiographically screened at 6 months of age. These hip radiographs were assessed for dislocation, and measurements were taken of the acetabular index and of the centre–edge angle of Wiberg.

The mean values for the acetabular index in breech infants were within normal limits. Infants with an acetabular index $>30^\circ$ were all stable on clinical examination at 6 months.

In conclusion, the current screening programme revealed no dislocated or displaced hips despite subjecting the patients to the hazards, inconvenience and cost of radiological screening at 6 months, and is of questionable value in paediatric orthopaedic practice.

Juvenile onset Crohn's disease in Scotland: increasing incidence and significant morbidity

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Scottish hospital in-patient statistics are collected prospectively on all admissions to National Health Service hospitals in Scotland (population 5.1×10^6 in 1988). We have used this database to monitor the incidence of juvenile onset (age ≤ 16 years) inflammatory bowel disease in Scotland and to derive geographically based samples to study the clinical features and surgical histories. There has been a sixfold increase in the incidence of juvenile onset Crohn's disease between 1971 and 1988, from 4.6 to 28.9 per 10^6 population aged ≤ 16 years. The incidence of juvenile onset ulcerative colitis has not changed significantly for the same period (approximately 16 per 10^6 population aged ≤ 16 years). Of the cohort of 67 patients with Crohn's disease with a mean follow-up period of 11.9 years, 48 have had 103 major operations. By life-table analysis, 50 per cent have had a major operation within 5 years of onset of disease, and 50 per cent of those having one operation have had a second operation within 5 years of the first. The crude permanent stoma rate is 28.3 per cent, and by actuarial analysis 14 per cent have a permanent stoma 5 years after onset, rising to 28 per cent at 15 years. Five patients have died. Of the 61 known to be alive, 51 (84 per cent) have been interviewed and examined. Crohn's disease activity index scoring showed that 35 (69 per cent) had inactive disease (score <150), ten had mildly active disease and six (12 per cent) had active disease (score >200), of whom one patient needed home parenteral nutrition. This study highlights the increasing incidence and significant morbidity of juvenile onset Crohn's disease in Scotland and provides sound information on prognosis for patients, their families and medical practitioners.

Melanoma in childhood and adolescence

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Melanoma in childhood and adolescence has a low incidence and has long been regarded as a relatively benign form. We report a retrospective study including 67 children with histologically verified melanoma treated at one of our institutions between 1974 and 1990.

The sex ratio (M:F) was 1:2 and the mean age was 17.8 (range 0.6–21) years. The tumour was localized at the extremities in 64 per cent ($n = 43$) and at the head, neck or trunk in 36 per cent ($n = 24$).

According to the pTNM classification, 21 per cent of the tumours ($n = 14$) were stage I, 39 per cent ($n = 26$) stage II, 24 per cent ($n = 16$) stage III, and 3 per cent ($n = 2$) stage IV. In nine patients (13 per cent) classification was not possible because of inadequate treatment before referral to our hospitals (pT_xN₀M₀). Surgical treatment was identical to the treatment for adult melanoma and followed the scheme of diagnostic excision and histological staging.

The overall mean (s.d.) 5-year survival rate was 69(7) per cent. It was 77(17) per cent for stage I patients, 84(9) per cent for stage II patients, 43(15) per cent for stage III patients, zero for stage IV patients and 88(17) per cent for patients in category pT_xN₀M₀.

We conclude that the prognosis of advanced melanoma in children and adolescents is as poor as in adults. Therefore, early diagnosis and adequate treatment are essential for a favourable outcome.

Role of ultrasonography in the diagnosis of acute appendicitis in children

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The diagnosis of acute appendicitis remains a challenge, especially in children. Several studies show that ultrasonography (US) is a valuable diagnostic tool in acute appendicitis. We wished to investigate the role of US in the diagnosis of acute appendicitis in paediatric patients.

Data on all children under the age of 16 years who underwent appendicectomy in our institution between 1 January 1980 and 31 December 1990 were analysed retrospectively. US was introduced in the investigation of patients with suspected acute appendicitis in November 1986 and, for our study, patients were divided into two groups. Patients in group 1 were operated on before 1 November

1986, and those in group 2 after this date.

In all, 815 children underwent appendicectomy in this period. In group 1 there were 585 children, 212 of whom (36.2 per cent) had an uninfamed appendix. Of 230 patients in group 2, 51 (22.2 per cent) did not have acute appendicitis. In this group, 125 (54.3 per cent) underwent US, the other 105 patients (45.7 per cent) being operated on without previous US for clinically apparent acute appendicitis. Thirty of these (28.6 per cent) had a normal appendix. US gave a true positive in 89 cases (71.2 per cent) and a false positive in four (3.2 per cent). Thirty-three children were operated on despite negative US; 17 were false negatives.

The number of perforated cases did not differ significantly in the two groups (10.6 cases per year in group 1 *versus* 8.5 cases per year in group 2).

We conclude that US helps to improve the diagnostic accuracy in acute appendicitis in children. In spite of a more restricted indication for appendicectomy in the period when US was used, the number of perforations did not increase as a result.

Pancreatic duct occlusion with fibrin sealant after pancreatic head resection

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Dehiscence of the pancreaticointestinal anastomosis occurs even when a healthy pancreatic tail is anastomosed to the intestinal tract. The incidence of postoperative fistula is 5–35 per cent. A reduction in these postoperative complications can be achieved by pancreatic duct occlusion (PDO) with prolamin: a quick and irreversible exocrine insufficiency results and the exocrine secretions which disturb the healing process are eliminated. However, there is still controversy concerning the risks of endocrine damage with PDO.

The aim of this experimental study in domestic pigs ($n = 28$) was to block the exocrine secretion only temporarily by PDO with fibrin sealant (FS) to ensure a safe protection of the anastomosis. Long-term studies up to 6 months after operation showed that a high local concentration of aprotinin (fibrinolysis inhibitor) of 20 000 units ml^{-1} added to the FS was necessary to block the exocrine secretion for the first 5 days after operation. In contrast to PDO with prolamin there was only a lower grade interstitial fibrosis of the exocrine tissue, with no damage to endocrine function. The healing of the pancreaticointestinal anastomosis was undisturbed.

So far, this new and effective method has been employed successfully in 67 patients undergoing Whipple's operation for carcinoma of the head of the pancreas. No pancreatic fistula has occurred and none of the patients has died. In the observation period up to 3 years, only three (4 per cent) of the 67 patients have become diabetic.

This method can be recommended for the protection of the pancreaticointestinal anastomosis in Whipple's operation (and pancreas transplantation).

Canine model to study exocrine pancreatic pathophysiology

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This model arose from the need to exert serial 'natural' stimulation of the pancreas rather than single 'unnatural' intraoperative mechanical and/or chemical stresses, as usually performed. The canine pancreas has two distinct limbs; the ventral is suitable for transplantation.

Thirty-eight mongrel dogs were operated on, employing the following technique. The lateral region of the neck was entered through a 15-cm incision along the anterior edge of the cleidocervical muscle, and a pouch was created by blunt dissection of the two skin flaps. The external jugular vein and common carotid artery were prepared. The pancreas was then exposed via a midline abdominal incision, and its two limbs divided; the main duct was identified and cannulated with a polyethylene catheter on the cut surface of the ventral part. The ventral pancreas was then removed with its vascular pedicle, perfused and transposed to the lateral cervical region. First the pancreatic arteries were anastomosed to the common carotid artery, and then the vein to the external jugular vein. The catheter was passed out of the incision.

Transplantation was successful in 37 cases (97 per cent). One failure occurred because of vascular necrosis. The transplanted pancreas with its permanently accessible excretory duct provides: (1) monitoring of pancreatic exocrine function; (2) possibility of modulation of intensity of selected stimuli; (3) ability to compare changes in the two divisions of the pancreas once the animal has been killed. This model is presently being employed to study the autoimmune aetiological theory of acute pancreatitis.

Protective effect of a mimic nitroxide of superoxide dismutase on lipid peroxidation in caerulein-induced acute pancreatitis in rats

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This study aimed to investigate the lipid peroxidation process in caerulein-induced acute pancreatitis and the effect of low molecular weight superoxide dismutase (SOD), a mimic nitroxide, on membrane penetration in this process.

Eighteen rats were divided into three groups: in group 1 six rats acted as controls; in group 2 six rats had infusion of a supramaximal dose of caerulein for 3 h at $10 \mu\text{g kg}^{-1} \text{h}^{-1}$; in group 3 six rats had an infusion of caerulein as in group 2 and simultaneously received 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy SOD mimic-nitroxide radical (3 ml 30 mmol l^{-1} solution over 3 h). Lipid hydroperoxides, which reflect the lipid peroxidation process, were measured by a modified tetramethylbenzidine method.

In group 2 an increase of 116 per cent in lipid hydroperoxide concentration was observed compared with controls (51 versus 110 nmol mg protein $^{-1}$). In group 3 the increase was only 43 per cent (51 versus 73 nmol mg protein $^{-1}$).

These data suggest that free radicals may play an essential role in the pathogenesis of caerulein-induced acute pancreatitis. A low molecular weight SOD mimic, membrane-penetrable nitroxide radical could be a potential therapeutic agent in acute pancreatitis.

Effects of Sandostatin on pancreatic blood flow, structure and function during the development of experimentally induced acute pancreatitis

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Since there are few data available on temporal changes in pancreatic blood flow (PBF) during the development of acute pancreatitis, we have carried out a study in rats to investigate PBF and the effects of Sandostatin (SMS). Pancreatitis was induced in male Wistar rats by common bile duct ligation and intravenous infusion of caerulein ($5 \mu\text{g kg}^{-1} \text{h}^{-1}$) for 2 h. Control rats received a subcutaneous injection of saline immediately before and 8 h after the induction of acute pancreatitis, and the experimental group were given 2 μg SMS subcutaneously. Organ blood flow (microsphere method), serum amylase levels and pancreatic structure were determined 4 and 16 h after the start of the study. The pancreas in the controls was oedematous 4 h after the induction of pancreatitis, and all animals displayed marked hyperamylasaemia. At 16 h the pancreas in the controls was haemorrhagic and necrotic, but the serum amylase levels were decreased. SMS ameliorated the change in both pancreatic structure and function at 4 and 16 h. SMS significantly ($P < 0.001$, ANOVA) reduced mean (s.e.m.) PBF (2.3(0.05) ml per min per gram dry weight) compared with control animals at 4 h (4.1(0.07)), but maintained pancreatic perfusion (2.1(0.04)) compared with the reduction observed in the controls (0.6(0.09)) at 16 h ($P < 0.001$).

The results of this study indicate that SMS prevents both early hypoperfusion and late hyperperfusion during the development of acute pancreatitis in the rat. Further studies are required to determine whether the changes in PBF elicited by SMS are responsible for its protective effect on pancreatic function and structure.

Effects of cimetidine on the permeability and morphology of the main pancreatic duct in cats

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The changes in permeability in the main pancreatic duct and the morphology of the pancreas of cats after exposure of the duct to cimetidine and after parenteral administration of this drug were studied.

Cats were anaesthetized and the main pancreatic duct was cannulated and perfused from the tail to the head of the pancreas. The duct was perfused at pressures which never exceeded 20 cmH₂O at a rate of 1 ml h⁻¹. The periods and the perfusion solution used in each group are shown in the Table.

	Control group	Group 1	Group 2
Period 1	SPS	SPS	SPS
Period 2	PS	Cimetidine	PS
Period 3	SPS	SPS	SPS

SPS, standard perfusion solution; PS, physiological saline

In group 1 cimetidine at an alkaline pH (8.4) was perfused through the main duct. In group 2, cimetidine was given intramuscularly at a dose of 25 mg kg⁻¹ four times daily for 5 days before the perfusion study. Chloride fluxes were determined in each group. At the end of each experiment a small segment of pancreas from the perfused lobe and the unperfused lobe were sent for histological examination.

The difference in net flux of chloride across the duct before and after exposure to cimetidine and after parenteral administration of cimetidine reflects damage to the mucosal barrier. We found that there was a negligible change in chloride flux and the permeability of the duct was stable for up to 3 h in each group. It was found that there was neither acute pancreatitis nor any histopathological difference between the perfused and unperfused ducts in each group.

Sandostatin ameliorates the deleterious effects of endotoxin on pancreatic structure, function and blood flow in rats

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Previous studies have shown that experimentally induced pancreatitis results in a systemic endotoxaemia that is ameliorated by Sandostatin (SMS). The aim of this study was to establish whether endotoxaemia resulted in changes in pancreatic structure, function and blood flow in the rat, and whether SMS influenced any of these effects. Groups of male Wistar rats received intraperitoneal endotoxin (20 mg kg⁻¹) or saline. Half of the animals in each group received SMS (2 µg subcutaneously) immediately before and 12 h after administration of endotoxin or saline. Organ blood flow (microsphere method), hepatic reticuloendothelial system (RES) activity (liver:blood ^{99m}Tc sulphur colloid), serum amylase and pancreatic structure were determined 16 h after the administration of endotoxin or saline. Endotoxin administration resulted in an oedematous haemorrhagic pancreatitis which was prevented by SMS. Mean (s.e.m.) pancreatic blood flow (1.06(0.06) versus 2.4(0.05) ml min⁻¹ g dry weight⁻¹; $P < 0.01$) and hepatic RES activity (4.33(0.44) versus 6.3(0.23); $P < 0.001$, ANOVA) were significantly less in rats treated with endotoxin compared with those treated with endotoxin plus SMS. SMS also prevented the hyperamylasaemia observed in rats treated with endotoxin. The results of this study indicate that endotoxin has a deleterious effect *per se* on pancreatic structure, function and blood flow in the rat that is ameliorated by SMS, thereby offering a partial explanation for its beneficial effect in experimentally induced acute pancreatitis.

Histochemical localization of xanthine oxidase in the canine pancreas

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Xanthine oxidase (XO)-generated toxic oxygen metabolites initiate the increased microvascular permeability seen in *ex vivo* canine models of acute pancreatitis. However, attempts at the biochemical assay of XO activity in the pancreas have been unsuccessful due to low levels, non-homogeneous distribution, and the confounding effect of resident proteases. We used the allopurinol-inhibitable and superoxide dismutase (SOD)-inhibitable conversion of nitroblue tetrazolium (NBT) to a blue formazan precipitate by superoxide radicals generated from oxygen and substrate (hypoxanthine) by active XO in 11 per cent polyvinyl alcohol as the basis for histochemical localization of XO in fresh frozen sections of dog pancreas. In ten pancreas glands, blinded grading revealed strong (median grade 2) staining localized exclusively to the endothelium and smooth muscle of the pancreatic microvasculature, with no staining whatsoever of the apocrine or exocrine parenchyma. This staining was abolished by XO inhibition with allopurinol in paired sections (grade 0, $P < 0.02$). Staining was also completely blocked by scavenging superoxide radicals with SOD. These findings clearly indicate that significant, superoxide-producing XO enzymatic activity in the canine pancreas is localized to the microvascular wall. This localization would explain the basis for the early microvascular injury mediated by toxic oxygen metabolites generated by XO in canine models of acute pancreatitis.

Gabexate mesilate in acute pancreatitis: an experimental study

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The aim of the study was to investigate the influence of synthetic antiprotease gabexate mesilate (FOY) on circulatory and respiratory disturbances complicating the early period of acute experimental pancreatitis. This was induced in 25 dogs by the injection method. Seven dogs received no therapy; 18 animals, divided into three groups, were treated with gabexate mesilate infusion (1 mg kg⁻¹ h⁻¹) 30 min before, 30 min after and 3 h after induction of pancreatitis respectively. The animals were observed for 10 h. During the experiment, haemodynamic values were monitored hourly using a Swan-Ganz catheter and arterial gases were measured. After the experiment lungs were collected for histopathological examination. FOY protected the animals from reductions in cardiac output, mean arterial pressure, left ventricular stroke volume and from increases in pulmonary and systemic vascular resistance. This was especially so in dogs receiving FOY prophylactically and 30 min after induction of pancreatitis. It also prevented decrease of arterial partial pressure of oxygen and histological alterations in the lungs. Interstitial oedema, thickened alveolar septa, focal atelectasis and intravascular thrombosis were observed in untreated animals. Our results indicate that gabexate mesilate prevents haemodynamic and respiratory disturbances in the early period of experimental acute pancreatitis.

Diagnostic and surgical procedures in acute necrotizing pancreatitis

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Pancreatic necrosis and sepsis are the major causes of death in acute pancreatitis (AP). Infectious complications are currently responsible for 80 per cent of deaths in patients with AP. Early diagnosis and prompt surgical treatment are necessary for survival of patients with this complication of necrotizing pancreatitis.

The purpose of this study was to analyse the results of surgical treatment in patients suffering from infected pancreatic necrosis complicating acute haemorrhagic pancreatitis.

Thirty patients were divided into two groups: group I (16 patients) were treated operatively in the years 1968–1985 and group II (14

patients) were operated on in 1986–1991. In group I, where pancreatic necrosis and infection were recognized after surgery, nine omental sac drainages, three pancreatectomies and four necrectomies were performed. In group II, after contrast-enhanced computed tomography and preoperative diagnosis of pancreatic necrosis and infection by fine needle aspiration biopsy were introduced, five patients underwent necrectomy with closed drainage and in nine patients Bradley's laparostomy was performed. The mortality rate in patients in group I was 80 per cent. The change in the clinical strategy diminished the mortality rate in group II to 50 per cent. Laparostomy proved to be the most convenient surgical procedure, with a mortality rate of 33 per cent.

Our results underline the importance of preoperative diagnosis of pancreatic necrotic infection and suggest that laparostomy should be considered as a method of choice in the operative treatment of infected pancreatic necrosis.

Surgical versus endoscopic and percutaneous therapy of pancreatic pseudocysts: a 5-year follow-up study

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Pancreatic pseudocysts is a frequent complication of acute or chronic pancreatitis which has to be taken seriously and which can be treated surgically, endoscopically, by percutaneous drainage or by a combination of these forms of therapy.

Between 1985 and 1990, 127 patients with pancreatic pseudocysts have been treated in our departments (44 surgically, 37 endoscopically, seven by percutaneous drainage only, 26 by combined treatment, 13 showed spontaneous regression) and re-examined after a period up to 33 months as to the success of therapy. Twelve patients had died in the meantime, 18 did not appear for re-examination. Of the remaining 97 patients, 50 per cent of those treated exclusively by surgery and 51 per cent of those treated exclusively by endoscopic drainage reported being free of symptoms or predominantly so.

Our results show that endoscopic drainage in both acute and chronic pseudocysts is worthwhile if there is no definite indication for surgery or percutaneous drainage. In case of failure or recurrence, surgical drainage or resection of the pseudocyst are indicated. Exceptions are very young patients, the presence of small pseudocysts, and continued alcohol abuse.

Improved surgical decision making for pancreatic pseudocysts

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Forty-three consecutive cases of pancreatic pseudocyst (PPC) were observed at this institution, 18 between 1970 and 1980 (group 1) and 25 between 1981 and 1990 (group 2). Elective surgery was undertaken in group 1 patients after 4–6 weeks of conservative therapy, and in group 2 when the thickness of the PPC wall was ≥ 4 mm as assessed by ultrasonography. Twenty-four patients had an internal drainage procedure (group 1, nine; group 2, 15), five had a distal pancreatectomy (group 1, one; group 2, four), one had a total pancreatectomy (group 1) and one had a Wirsung jejunostomy (group 2). External drainage was required in nine patients (group 1, seven; group 2, two). In three patients (group 2) spontaneous regression of the PPC was observed using ultrasonography. Internal drainage could not be performed in four patients in group 1 because of an inadequate PPC wall; in group 2 this procedure was always possible, with ultrasonography giving a PPC wall thickness of ≥ 4 mm.

The postoperative stay was 47.8 days after external drainage and 20.2 days after internal bypass. There were two postoperative deaths (5 per cent) and nine major complications (20 per cent): four pancreaticocutaneous fistulae (group 1, three; group 2, one), two pancreaticointestinal fistulae (group 2), one case of haemorrhage (group 1), one case of jaundice and severe cholangitis (group 1) and one case of pancreatic ascites (group 1). In 30 patients (75 per cent) the postoperative course was uncomplicated.

The results can be summarized as follows: (1) the thickness of the PPC wall is the major indicator that the pseudocyst is ready for internal drainage; (2) ultrasonography allows accurate assessment of PPC wall thickness; and (3) timing the operation by PPC wall thickness reduces the duration of treatment and optimizes results.

Multiple organ failure in patients with acute pancreatitis

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The aim of this study was to assess to what degree the treatment of patients with severe haemorrhagic-necrotic pancreatitis (HNP), in intensive care units, influenced both their survival and the development of multiple organ failure (MOF). Studies were conducted based on retrospective assessment of acute pancreatitis (AP) patients in 1974–1979 (period I) and 1980–1990 (period II). This grouping follows establishment of intensive care units. Patients were grouped according to sex, form of disease, therapeutic method, etc. The number and type of failing organs was also noted. In 1974–1990 a total of 261 patients with AP, including 121 men and 140 women, were subjected to treatment. In periods I and II there were 61 patients (23 men and 38 women) and 200 patients (98 men and 102 women) respectively. In period I, 32 patients underwent surgery, and 15 had HNP, with 17 having oedematous pancreatitis. In period II, 30 patients underwent surgery, including 24 with HNP. Another 24 patients with HNP received conservative treatment. In period I about 40 per cent of patients (six) with failure of two organs survived, and in most cases the failures were either circulatory or respiratory. In the following years, in addition to a considerable increase of survival time (up to 233 days) in most severely ill patients, a failure of one to six organs was found (in the forms of hepatic failure, renal failure, bleeding into alimentary tract, haemorrhagic diathesis, sepsis and encephalopathy). The majority (32 patients) survived, some with failure of five and six organs. No patient who experienced severe shock survived.

In conclusion, the treatment of patients with severe HNP in intensive care units considerably lengthened their survival time. This led to the development of MOF, but despite development of MOF a decrease in mortality rate in period II was observed.

Prevention of acute pancreatitis and leakage after pancreaticoduodenectomy

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Acute pancreatitis and leakage of the pancreaticojejunal anastomosis are the most important causes of operative morbidity and mortality after pancreaticoduodenectomy. Several attempts have been made to avert these complications, by such means as ligature or injection of sclerosing substances into the Wirsung duct, or by alternative operative procedures. We have devised and employed a new technique for pancreaticoduodenectomy utilizing several modifications during the reconstruction phase. After pylorus-preserving pancreaticoduodenectomy according to Traverso and Longmire, the pancreaticojejunostomy is made on a separate loop with respect to the duodenojejunal and hepaticojejunal anastomoses. The duodenojejunal anastomosis is proximal to the hepatic one to avoid a continuous biliary reflux into the stomach.

Since June 1988, 14 patients (nine men, five women) have undergone surgery for chronic pancreatitis and periampullary neoplasms. No patient died in the postoperative period and no leakage from pancreatic anastomosis occurred in our series.

To date, in no case have we encountered acute pancreatitis in the pancreatic remnant. In one patient, hepaticojejunostomy leakage occurred in the early postoperative period; this case of biliary fistula was treated conservatively. The long-term results confirm normal digestive physiology without dumping syndrome, peptic ulceration or enterogastric reflux.

In conclusion, we believe that the proposed method of reconstruction integrates the demands of security (prophylaxis of pancreatitis and leakages) with function (prophylaxis of enterogastric reflux).

Solid papillary neoplasm of the pancreas: report of a case

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Solid papillary neoplasm of the pancreas is an extremely rare tumour with a predilection for young women. Its low incidence ranges from

0.2 to 2.7 per cent of non-endocrine pancreatic cancers. Only 27 well documented cases have been reported in the literature. Its histogenesis remains a matter of controversy.

The case of a 28-year-old woman with a 1-year history of epigastric pain is reported. Clinical examination was normal. Computed tomography revealed a tumour with solid cystic areas located in the tail of the pancreas.

The patient underwent distal pancreatectomy and splenectomy. After operation a low output pancreatic fistula resolved in 1 week. Grossly, the tumour appeared well circumscribed and measured 10 cm in diameter. On cross-section, it was multilocular with solid yellow areas discoloured from haemorrhage. Microscopically, the tumour was composed of polygonal cells with eosinophilic granular cytoplasm and round to oval nuclei with a low mitotic rate. There was a solid pseudopapillary pattern around blood vessels. Many cystic areas, with fibrin clots inside, showed cholesterol deposits and histiocytes in the wall of the cysts. Immunohistochemical staining for α -antitrypsin and prekeratin were positive.

The findings support an origin from exocrine pancreas. The diagnosis was compatible with solid papillary tumour of the pancreas. Nine months after surgery the patient has no evidence of recurrence. Long survival or even cure can be expected, but the accumulated experience from the literature indicates that this neoplasm should be regarded as a low grade, potentially malignant, tumour.

Cystic pancreatic tumours

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Cystic pancreatic tumours are a rare entity and require to be differentiated from adenocarcinoma and pseudocysts. The purpose of this communication is to present our experience.

Five patients (three men, two women) aged 36–73 years have been studied. Past history showed that two had diabetes and one had asymptomatic hyperglycaemia. Epigastric pain was the main complaint, present in four cases. A palpable abdominal mass was evident in two patients and the fifth was diagnosed as an incidental finding at ultrasonography (US).

Diagnostic methods included abdominal US in all cases and computed tomography in three patients, with guided percutaneous needle biopsy in two of them. Surgical treatments performed were two pancreaticoduodenectomies, two distal pancreatectomies and one total pancreatectomy.

Histological examination demonstrated three cystadenomas and two cystadenocarcinomas. One patient, operated on for a malignant neoplasm, died on the 14th day after operation with a massive upper gastrointestinal haemorrhage. Another case suffered pneumonia and was discharged in good health. A malignant recurrence developed in the other case of cystadenocarcinoma, which caused his death 1 year later.

We consider it essential to remove surgically every cystic pancreatic tumour because of the difficulty in preoperative diagnosis of malignancy. Excellent results are achieved in benign lesions.

Influence of antrectomy on the somatostatin D cell population of pancreatic islets: a morphometric study

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This experimental study was undertaken to establish a better understanding of adaptive mechanisms in pancreatic somatostatin-producing cells following antrectomy, and investigates the importance of duodenal alimentary stimulus.

Thirty male albino Sprague–Dawley rats were randomized: group 1, antrectomy and gastroduodenostomy; group 2, antrectomy and gastrojejunostomy; and group 3, control. The rats in all groups were killed 30 days after surgery, and pancreatic samples were obtained. These were stained immunohistochemically (avidin–biotin affinity technique) and somatostatin D cells were identified and counted. Morphometric evaluation was performed with an automatic image analyser.

The number and mean area of Langerhans islets was similar in the three groups. The mean pancreatic insular area decreased significant-

ly in the groups undergoing antrectomy. The number of D cells per islet and the number of D cells per mm² of pancreas decreased significantly in group 2 in relation to group 1 and the control group.

Our results indicate that antrectomy does not significantly alter the number of Langerhans islets or their mean area. The decrease in the mean area seen in groups 1 and 2 suggests an increase of exocrine pancreas. Gastrojejunostomy implies duodenal exclusion and this seems to be a determining factor in pancreatic endocrine adaptation as there were fewer pancreatic D cells in group 2.

Advantages of pylorus-preserving pancreaticoduodenectomy in malignant disease of the pancreas and periampullary region

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The aim of this study was to confirm pylorus-preserving pancreaticoduodenectomy (PPPD) as a safe and radical procedure in malignant disease of the head of the pancreas and periampullary region, with morbidity and mortality the same as or lower than the standard Whipple procedure (WP).

During the period 1984–1990, WP ($n = 44$) or PPPD ($n = 47$) was performed in 91 patients. Mortality rate in hospital was 2 per cent after PPPD and 5 per cent after WP. Median duration of resection performed and median blood loss in the PPPD group were 210 min and 1800 ml, respectively; after WP these figures were 255 min and 2500 ml (both differences $P < 0.01$).

No difference was found during follow-up of mean duration 25.2 (range 1–67) months, with respect to days of gastric suction, liquid diet, normal diet, complaints of, or medication for, ulcer disease, postoperative complications, recurrence of disease and survival. All patients had similar tumour node metastasis staging; the number of tumour-containing duodenal or gastric resection margins did not differ in either group of patients (two patients after PPPD, two after WP). Hospital stay was significantly ($P = 0.02$) shorter after PPPD, median 14 days compared with 18 days after WP. Weight gain after operation was significantly ($P = 0.01$) better after PPPD.

In conclusion, PPPD is a safe and radical procedure for cancer in the head of the pancreas or periampullary region, with the same survival and appearance of locoregional recurrence and distant metastases as after standard Whipple resection. The advantages of PPPD are that it is an easier and less time-consuming operation, with lower blood loss, is associated with a shorter stay in hospital and a better weight gain during recovery.

Pylorus-preserving pancreaticoduodenectomy

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In this study, the early and late results of pylorus-preserving pancreaticoduodenectomy were investigated in patients undergoing operation for periampullary malignancy.

Since January 1987, eight patients (seven men and one woman, aged 43–61 years) have undergone operation for periampullary malignancy with pylorus-preserving pancreaticoduodenectomy. The margin of resection of the duodenum was approximately 2 cm distal to the pylorus. Reconstruction was by antecolic end-to-side duodenojejunostomy using a two-layer anastomosis. These patients have been followed for a mean of 25 (range 2–58) months after operation. Symptoms were evaluated by careful questioning at follow-up. Barium examination of the upper gastrointestinal tract was obtained routinely.

The mean operation time was 7 h 10 min, the mean quantity of blood transfused 1.7 units, and the postoperative nasogastric decompression time 4–7 days. In 6 months, five of eight patients have regained weight and achieved their preoperative weight. Five patients developed complications: one wound infection and pleural effusion, two cases of isolated infection, one delayed gastric emptying, one intra-abdominal abscess, and one incisional hernia. There was no operative mortality. One patient who had lymph node metastases at operation died 14 months after operation with liver metastases.

The complications seen after classical Whipple's procedure, such as dumping syndrome, alkaline reflux gastritis, weight loss, jejunal ulceration and perforation, and gastrointestinal haemorrhage, were

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not seen in the present series. Thus, we believe that pylorus-preserving pancreaticoduodenectomy is the operation of choice for periampullary malignancy.

Pylorus-preserving pancreaticoduodenectomy in patients with periampullary carcinoma or ductal carcinoma of the head of the pancreas

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Pylorus-preserving pancreaticoduodenectomy (PPPD) has received increasing attention as a more physiological alternative to standard pancreaticoduodenectomy (PD) in patients with adenocarcinoma of the pancreas head (PC) or the periampullary region (PAC). We evaluated mortality, morbidity and survival in 110 patients with PAC ($n = 57$) or PC ($n = 53$). In each group 32 patients underwent PD; the remainder had a PPPD. There were no significant differences in age, sex, risk factors or tumour stage (Union International Contra la Cancrum 1987) between patients undergoing a PPPD or a PD. Median follow-up was 42 (range 3–62) months. Survival curves were calculated according to the Kaplan–Meier method.

There were no significant differences in mortality (1.8 per cent) and morbidity rates between procedures. The mode of resection had no significant influence on the survival rate of patients with PAC. Patients with PC who had a PD had a significantly improved survival rate compared with those who underwent a PPPD ($P < 0.05$), particularly those patients with advanced tumours, i.e. stage III ($P = 0.007$).

In patients with ductal carcinoma of the head of the pancreas a standard PD provides better survival than PPPD. However, PPPD appears to be an oncologically equivalent alternative to the PD in patients with PAC.

Pancreaticogastrostomy: a safe drainage procedure after pancreaticoduodenectomy

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The propensity for leakage and disruption at the site of pancreaticojejunostomy is a major cause of morbidity and death after pancreaticoduodenal resection. The purpose of this study was to evaluate the role of pancreaticogastrostomy as an alternative method of restoring pancreaticointestinal continuity after pancreaticoduodenectomy.

From January 1989 to September 1991, 26 patients underwent pancreaticogastrostomy after pancreaticoduodenectomy at this institution. Sixteen patients were men, and ten women. The mean age was 60.5 (range 42–74) years. Pancreaticoduodenectomy was performed for pancreatic carcinoma (13 patients), ampullary carcinoma (nine), duodenal carcinoma (two) and chronic pancreatitis (two).

There were two operative deaths, giving an overall operative mortality rate of 8 per cent; three patients had postoperative complications, an overall morbidity rate of 12 per cent. There were three pancreatic leaks (two stopped spontaneously on the eighth postoperative day and one required surgical drainage). All three healed completely. The mean postoperative hospital stay was 14 days.

These results agree with data published in literature. Trypsin neutralization by gastric acidity may explain the very low incidence of pancreatic fistula reported. In long-term follow-up, exocrine pancreatic insufficiency does not seem to occur. Radiological and endoscopic examination of the pancreatic duct is easy. This method of reconstruction merits widespread utilization; it is both simple and safe.

Criteria for resection of carcinoma of the body and tail of the pancreas

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Many surgeons regard carcinoma of the body of pancreas as incurable and generally irresectable at presentation. We have studied 24

patients with carcinoma in this site to determine the criteria for resectability.

Resection was performed in 13 patients and was not possible in 11. Many tumours were detected by ultrasonographic examination but determination of operability rested on angiography and computed tomography (CT). CT predicted inoperability in four of six cases and angiography in six of six cases. CT signs were lymph node enlargement and extension of the tumour mass. Angiography predicted inoperability when vascular encasement or occlusion was seen.

Resectable tumours were smaller, although occlusion of the splenic artery or splenic vein did not always prevent resection.

All patients with locally inoperable tumours died within 12 months. Median survival after resection (left resection seven, total pancreatectomy six) was 26 (range 3–40) months. Six patients survived 2 years.

CT evidence of retroperitoneal extension or perivascular lymph nodes and angiographic evidence of involvement of superior mesenteric artery, superior mesenteric vein, or coeliac axis indicate inoperability. In the absence of these signs, laparotomy with a view to resection of tumours of the body and tail of the pancreas is worthwhile.

Surgical treatment of secondary pancreatic infections: review of 40 cases

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We have studied the results of the surgical management of secondary pancreatic infections, with particular reference to the role of open treatment. The hospital records of 40 patients who underwent emergency operation for unequivocal secondary pancreatic infections between 1981 and 1991 were retrospectively reviewed. Patients were divided into two groups according to the type of surgery performed: closed treatment ($n = 24$), open treatment ($n = 16$). APACHE II score, postoperative morbidity and mortality rates were evaluated in both groups. The Fisher test and Student's t test were adopted for statistical analysis.

Both closed and open treatment groups had similar mean (s.d.) APACHE II scores (17.1(6.0) and 17.9(7.2) respectively) and type of supportive care administered, which included in all cases heavy doses of broad-spectrum antibiotics and total parenteral nutrition; the incidence of major surgical complications was 8 per cent (haemorrhage, one; fistula, one) versus 50 per cent (haemorrhage, three; fistula, four; colonic necrosis, one) ($P = 0.0004$); signs of recurrent or persistent sepsis were observed in 42 per cent ($n = 10$) versus 6 per cent ($n = 1$) ($P = 0.001$); overall mortality rate was 33 per cent ($n = 8$) versus 25 per cent ($n = 4$) (P not significant); mortality due to persistent or recurrent sepsis was 29 per cent ($n = 7$) versus 6 per cent ($n = 1$) ($P = 0.008$).

It is concluded that although the frequency of major surgical complications after open treatment is significantly higher than that observed after closed treatment, open drainage permits a better control of pancreatic infection, thus reducing the rate of mortality due to persistent or recurrent sepsis.

Treatment of adenocarcinoma of the pancreas with somatostatin and gonadorelin

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Experimental studies have shown a significant inhibition of adenocarcinoma of the pancreas by gonadorelin and somatostatin.

The aim of this prospective randomized controlled study was to examine the potential value of somatostatin (250 µg every 8 h), gonadorelin (3.75 mg monthly), or the two combined. One hundred and sixty-three patients with adenocarcinoma of the pancreas not resected for cure were divided into four groups which did not differ in terms of clinical, biochemical or pathological data.

The mean survival times were 6.0 months in the gonadorelin plus somatostatin group, 5.5 months in the gonadorelin group, 4.3 months in the control group and 3.8 months in the somatostatin

group. However, life-table analysis for all these groups of patients, and for patients grouped according to sex, lymph node involvement and metastatic spread, did not differ from one group to another. Improvement of patient status was observed in 20 per cent of patients receiving hormone therapy; no difference was noted between the treatment regimens.

These disappointing results may be explained by the extent of the pancreatic carcinoma in the patients studied. They suggest that different hormone therapy regimens might be considered according to the age and sex of patients, as well as to the presence or absence of hormone receptors.

Treatment of pain in cancer of the pancreas

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Pain from pancreatic cancer is severe and debilitating. The purpose of this study was to analyse the results of pain treatment in 37 patients with cancer of the pancreas who were divided into three groups.

Group 1 ($n = 20$) was treated by alcohol coeliac plexus blockade. Group 2 ($n = 10$) was treated by continuous morphine infusion to the epidural space. Group 3 ($n = 7$) was treated by morphine infusion to the intrathecal space. The mean follow-up time was 8 months.

Pain measurements, doses of morphine, supplementary analgesia requirements and adverse effects were recorded. The mean consumption of epidural morphine (group 2) was $11.72 \text{ mg } 24 \text{ h}^{-1}$ and of intrathecal morphine (group 3) was $4.68 \text{ mg } 24 \text{ h}^{-1}$ during the first 3 months of treatment. Pain relief was efficient in all the groups at the start of treatment. Pain relief obtained in group 1 was statistically significant after 3 months of treatment, and was good throughout the study. No clinical respiratory depression was observed. Nausea and vomiting were observed in groups 2 and 3.

Coeliac plexus blockade is a simple, effective and safe means of palliation. We believe that it should be considered more often.

Comparison of the early prognostic values of computed tomography and serum and peritoneal amylase and lipase determinations in acute pancreatitis

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This prospective study compares outcome with computed tomography (CT) findings and serum and peritoneal amylase and lipase determinations, both performed early in the course of acute pancreatitis (AP).

Between 1985 and 1990, 92 patients admitted for AP had peritoneal lavage (with 1 litre NaCl 0.9 per cent) and CT performed within 24 h of admission. There were 64 men and 28 women, median (range) age 41 (19–90) years; three causes of AP were identified: biliary lithiasis (19), alcoholism (54), and idiopathic factors (19). There were three deaths.

Outcome was assessed by considering two groups: mild forms (no complications nor stay in intensive care unit, 56), and severe and lethal forms (36). CT findings focused on the presence (57) or absence (35) of extrapancreatic spread (EPS). Each patient was given an enzymatic score (ES) which reflects the predominance of the serum or peritoneal concentration of the two enzymes. This score can be either 0, 1, or 2; ES = 0 if neither enzyme is present in the peritoneal fluid (found in 19), ES = 1 if amylase or lipase alone are present (27), and ES = 2 if both enzymes are present (46).

This study found that when prognosis provided by CT or enzyme determinations was favourable (i.e. no EPS on CT or ES = 0 or 1, respectively), approximately 80 per cent had a benign evolution (29 of 35 or 36 of 46 respectively). On the other hand, if information provided was unfavourable (i.e. EPS present or ES = 2), approximately 50 per cent will have a severe or lethal outcome (30 of 57 or 26 of 46, respectively). CT and enzyme determinations appear to be of roughly equal value in the prognosis of AP.

Comparison between two prognostic tables for acute pancreatitis (Ranson and Imrie)

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The aim of this study was to establish the utility of the two most common prognostic classifications of acute pancreatitis (Ranson and Imrie).

Over a 4-year period 138 patients with acute pancreatitis diagnosed on the basis of clinical, biochemical and computed tomographic findings have been studied prospectively. The score assigned by each system has been assessed for ability to predict complications.

Classification of pancreatitis	Ranson		Imrie	
	≥3 criteria	<3 criteria	≥3 criteria	<3 criteria
Fatal, infected collection, pseudocyst or multiple organ failure				
Present	55	18	58	24
Absent	21	44	15	41
Fatal or infected collection				
Present	24	0	24	0
Absent	52	62	58	56
Fatal				
Present	15	0	15	0
Absent	61	62	67	56

The Table indicates how well each system was able to differentiate patients with an increasingly grave clinical outcome.

Both the Ranson and Imrie classifications of acute pancreatitis have been found to be useful, with a global index of prediction of 71.0 and 71.7 per cent, respectively, and 100 per cent sensitivity for fatal cases for both classifications.

Biliary acute pancreatitis: correlation between papillary obstruction, clinical severity and pancreatic pathology

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The search for aetiological and pathogenic factors and the pathological-clinical correlation in biliary acute pancreatitis (BAP) is still the subject of research and, sometimes, of controversial results. We have studied 78 patients with BAP whose diagnosis and classification were made according to the combined index, and determined by ultrasonography, laparotomy and/or peroperative cytology.

A total of 66 patients was operated on. This was the study group in whom we could evaluate the initial severity, the presence of papillary and/or choledocholithiasis (CL), brief papillary obstruction (BPO) of < 48 h duration, a persisting obstruction (PPO) lasting longer and even until surgery, and pathology of the pancreas (oedema or necrosis).

We found 29 cases of gallbladder lithiasis with oedema (44 per cent) and six gallbladders with stones and necrosis of the pancreas (9 per cent); 27 patients had stones in the gallbladder and CL with oedema of the pancreas (41 per cent) and four patients had stones in the gallbladder and bile duct with pancreatic necrosis (6 per cent) ($\chi^2 = 0.15$, P not significant).

The association between BPO and oedema was present in 24 cases (36 per cent), BPO and necrosis in five (8 per cent), with only one death. The association between PPO and oedema was present in ten cases (15 per cent) and between PPO and necrosis in four (6 per cent) ($\chi^2 = 19.85$, $P < 0.05$). The association between PPO, clinical severity and necrosis was found in only one case (2 per cent).

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Fifty-four of mild and moderate cases suffered oedema (77 per cent) and five suffered necrosis (8 per cent). Of the severe cases six had oedema (9 per cent) and four had necrosis (6 per cent).

In conclusion, severe BAP produces oedema more frequently (60 per cent) than necrosis (40 per cent); $P < 0.001$. PPO tends to produce oedema (71 per cent, ten of 14 cases) more frequently than necrosis (29 per cent, four of 14); $P < 0.05$. There was no direct correlation between papillary obstruction, clinical severity and pancreatic necrosis in BAP.

Conservative medical and surgical treatment of acute necrotizing pancreatitis: report of a series of 412 patients

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Surgical treatment of acute necrotizing pancreatitis (ANP) is still controversial. Aggressive, extended ablative procedures have encountered high mortality rates. Since the early 1980s a more conservative approach has been proposed.

In this series, our policy has been to wait as long as possible before operating in severe cases of ANP; medical treatment, ultrasonography and contrast-enhanced computed tomography have been carefully completed to establish the best time for surgery. Between January 1984 and October 1991, 412 patients were treated for acute pancreatitis at our centre: of these, 130 were suffering from ANP; 82 of the latter were treated conservatively with 11 per cent mortality rate (nine patients) and eventually underwent surgery for their biliary lithiasis, where indicated.

The last 71 patients underwent early endoscopic retrograde cholangiopancreatography followed by sphincterotomy with no deaths.

Forty-eight patients required surgery for ANP. Surgical procedures varied from necrectomy to major pancreatic resection. The overall mortality rate was 23 per cent (11 patients).

Our data confirm that a more conservative approach to ANP may lead to lower mortality rates. Surgery was always undertaken on the basis either of needle confirmation of sepsis or of extensive pancreatic necrosis together with poor persisting clinical status at least 3 weeks after the onset of the disease ('failure to improve').

Treatment of postoperative pancreatic and enterocutaneous fistulae with total parenteral nutrition and somatostatin

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The efficacy of total parenteral nutrition (TPN) and somatostatin was assessed in reducing output and promoting healing of postoperative pancreatic and enterocutaneous fistulae. Somatostatin was administered intravenously at $3.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ after starting TPN, and continued for 2 days after spontaneous fistula closure or until surgical reintervention was indicated.

In a consecutive series of 23 patients (aged 16–69 years), six presented with persistent postoperative external pancreatic fistulae and 17 with enterocutaneous fistulae (five duodenum, three jejunum and nine ileum). Closure was achieved in 19 patients (83 per cent) after a mean(s.d.) fistula duration of 11.0(7.9) days and a mean(s.d.) of 13.2(7.0) days of drug treatment. No mortality was observed. After the first day of combined therapy, fistula output was reduced by 69 per cent ($P < 0.001$). In 60 per cent of cases the fistula output fell to <50 per cent of the initial level. The response to combined therapy was unrelated to age and sex, location in the gastrointestinal tract, and duration or daily output of the fistula before institution of the combined therapy. Infection of the fistula markedly prolonged the fistula closure time, but did not affect overall outcome. In three of the four fistulae which failed to close a mechanical obstruction could be identified and was successfully operated on without mortality.

Somatostatin has been shown to be useful in the conservative treatment of pancreatic and enterocutaneous fistulae because of its ability to reduce output significantly and to accelerate closure.

Surgical treatment of necrotizing pancreatitis by open or closed abdomen

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During the 5-year period from 1986 to 1991, 13 patients with necrotizing pancreatitis were treated surgically in our department. Eight patients underwent necrectomy, closure of the abdomen and postoperative lavage of the lesser sac (group A). In the remaining five patients (group B) necrectomy was followed either by placement of an abdominal zipper (three cases) or by anchoring the stomach and transverse colon to the upper and lower flaps of the incision respectively and leaving the abdomen open (two cases).

Five patients in group A died in the immediate postoperative period (mortality rate 63 per cent), one survived but developed a large pseudocyst, and the remaining two had a relatively uneventful course and are well 10 and 12 months after surgery. Among the group B patients, two died after surgery (mortality rate 40 per cent) and three survived with no major complications and are well 30, 18 and 6 months after the operation. Mean hospitalization time was 60 days for group A and 90 days for group B patients. The mean number of reoperations was 1.3 for group A and 3.1 for group B.

We conclude that the technique of the 'open abdomen' for the treatment of acute necrotizing pancreatitis may increase survival compared with that after the 'closed abdomen' technique, but is followed by an increased number of reoperations and a prolonged hospitalization time in the intensive care unit.

Surgical treatment of acute pancreatitis

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In the treatment of acute pancreatitis (AP) the choice and timing of surgery is controversial.

In the 10 years from 1981 to 1991, 135 patients with AP were observed. The study included evaluation for multiple organ failure, imaging, and use of a multiparametric system for prognosis and surgical treatment.

Mean scores on prognostic index were Ranson 2.8 points, APACHE II 11.4; there was one organ failure in 60 per cent and multiple organ failure in 33 per cent of patients.

In 75 patients (56 per cent) surgical treatment was performed for worsening of clinical symptoms, extended pancreatic necrosis in stable patients, infected necrosis or abscess and biliary stones.

Surgical treatment of the pancreatic lesion was necrectomy or sequestrectomy and retroperitoneal drainage-lavage; biliary pathology was treated with cholecystectomy and drainage of the biliary tree was required.

Fifteen patients died and mortality was from multiple organ failure and local sepsis.

In conclusion, we have achieved our therapeutic goals: to identify the degree and evolution of pancreatic lesion; prevent organ failure; work out the optimal timing; optimize necrectomy and institute retroperitoneal drainage-lavage.

Role of prostaglandin E_2 in acute necrotizing pancreatitis and its relationship to treatment with somatostatin

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Acute necrotizing pancreatitis (ANP) constitutes a major medical and surgical problem. Although different drugs have been tested, controversial results have been obtained, probably because it is difficult to obtain standardized groups. Somatostatin (SS) has been demonstrated to reduce pancreatic output among other theoretical effects in ANP, and it has been clinically evaluated with different results. This study presents the results obtained with SS treatment of ANP, and the relationship with portal and systemic levels of prostaglandin E_2 (PGE_2) in an experimental model of ANP.

The experimental model chosen was transduodenal canalization of the common biliopancreatic duct of the rat with perfusion of 5 per cent taurocholic acid at 0.1 ml min^{-1} for the same number of minutes

as hundreds of grams of weight of the animal. This experimental model produces ANP with a 100 per cent mortality rate before 36 h. Ten Wistar rats of weight range 335–353 g were randomly assigned to each subgroup. *Group A (control group)*: A1: normal values of portal and systemic levels of PGE_2 were obtained by direct puncture of inferior vena cava and portal vein; A2: saline infusion of common biliopancreatic duct was carried out at the same flow rate. Blood samples were obtained at 0 h; A3: same as A2, but samples were obtained at 6 h. *Group B (ANP)*: after the production of ANP a central line via the external jugular vein was placed, and saline infusion at 0.1 ml h^{-1} started. Venous samples as in group A were obtained at 0 (B1), 6 (B2), 12 (B3) and 24 h (B4). *Group C (treatment)*: SS infusion at $4 \mu\text{g kg}^{-1} \text{ h}^{-1}$ was started after 12 h of ANP evolution. Blood samples were obtained at 6 (C1), 12 (C2), 18 (C3) and 24 h (C4) after SS infusion was started.

Portal and systemic levels of PGE_2 were raised in control (A2) and ANP (B1) groups, but immediate normalization ($P < 0.05$) was achieved in the control group. PGE_2 evolution in ANP group showed progressive decrease from raised levels, and at death rats show PGE_2 levels below normal. In the treated group, PGE_2 levels remained raised ($P < 0.01$), with no mortality. Statistical significance was found for differences between A2–B1, A3–B2 and B4–C3 (groups with similar time of evolution). In conclusion, a relationship between ANP and portal and systemic levels of PGE_2 was found. The beneficial effect of SS in this experimental model of ANP can be mediated by PGE_2 , PGE_2 and SS together can give added beneficial effects to treat ANP in this model.

Pancreatic abscess and acute biliary pancreatitis

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In Chile, biliary lithiasis is the main cause of acute pancreatitis and pancreatic abscess formation which is the most frequent complication. The aim of this study was to analyse the incidence, symptoms and signs as well as the results of surgery in pancreatic abscess of biliary origin.

The treatment programmes of 56 cases of acute pancreatitis admitted to the intensive care unit between 1988 and 1990 were reviewed. Within this group 38 cases (68 per cent) were of biliary origin; 17 of these cases (45 per cent) presented with pancreatic abscess. Infected pseudocysts were excluded. On admission, 43 per cent of cases had a Ranson score < 3 with 15 cases (83 per cent) having had previous biliary surgery. In 47 per cent of cases the diagnosis was made on clinical grounds alone.

All patients underwent surgery, 29 per cent before the second week. In 11 cases necrectomy was performed; in five of these laparostomy was also attempted. Ten patients required reoperation.

The most frequent postoperative complications were: multisystem malfunction (11), intra-abdominal abscesses (four) and pancreatic fistulae (three).

The overall mortality rate was 41 per cent, which reached 50 per cent in patients requiring reoperation more than twice, and 55 per cent for those having a Ranson score ≥ 3 . More recently our results have improved. We would like to highlight the high incidence of pancreatic abscess in acute biliary pancreatitis, especially in patients with a history of previous biliary surgery. This abscess is formed at the outset independently of the Ranson score.

Glucagonoma: report on one resected case

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A 50-year-old woman with no significant past medical history presented with a pruritic erythematous squamous dermatosis resistant to all treatments. The diagnosis of necrolytic migratory erythema was made 9 months later. The patient experienced weight loss of 2 kg. Biochemical testing revealed hypoalbuminaemia, hypoamino-acidaemia and hyperglucagonaemia of 324 pmol l^{-1} (normal range $14\text{--}72 \text{ pmol l}^{-1}$). Abdominal ultrasonography revealed a

hypoechoic nodule 1.7 cm in diameter in the tail of the pancreas. The computed tomography (CT) scan indicated a homogeneous tissue density mass, with peripheral calcifications. Angiography revealed hypervascularization of this mass arising from the splenic artery. The search for polyadenomatous tumours was negative. Laparotomy revealed a firm tumour 6 cm in diameter in the tail of the pancreas. A splenectomy and distal pancreatectomy was performed. The patient had an uncomplicated postoperative course.

On electron microscopy, the tumour cells contained typical glucagon granules. Capsular infiltration and lymphatic emboli were noted.

Two hundred cases of glucagonoma have been reported since 1942. Glucagonoma is an endocrine tumour which develops in the α -cells of the islets of Langerhans and grows slowly. It is usually located in the left part of the pancreas (62 per cent of cases). Malignancy is frequent (70–80 per cent of cases). Radical surgical resection of the tumour and its possible hepatic metastasis is the treatment of choice. When total resection is impossible, partial resection is indicated to optimize the efficacy of chemotherapy (by dacarbazine). Chemotherapy is also justified in pancreatic tumour recurrence after surgery or hepatic metastasis. The longest survival reported in the literature is about 4 years.

Latex tunnel and median laparostomy: an efficient method for drainage of pancreatic necrosis

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Experience with the treatment of acute necrotic pancreatitis is presented, together with an evaluation of different methods of peritoneal drainage after surgery. A total of 157 patients underwent surgery: 28 (17.8 per cent) by subtotal pancreatectomy, 36 (22.9 per cent) by necrectomy and sequestrectomy and 93 (59.2 per cent) by various conservative procedures (exterior drainage, pancreatic decapsulation and different operations according to aetiology). In this series, the mean mortality rate was 16.6 per cent, with the highest percentage (57.1) among patients undergoing subtotal pancreatectomies.

The last ten patients (6.4 per cent) were treated by the procedure termed 'intraperitonealization' of the pancreas, combined with external drainage of the pancreatic site by a tunnel of latex accompanied by a median laparostomy. The latex tunnel was removed after 10 days. The residual cavity remains in communication with the exterior by the laparostomy, by which it is possible to continue to wash the anterior part of the pancreas. Employing this procedure, we were able to reduce the mortality rate to 10 per cent.

Effect of pancreaticobiliary duct obstruction on organelle fragility and pancreatic energy metabolism in rats: protective effect of E3123

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The aim of this study was to examine the mechanism of pancreatic injury in rats with common channel obstruction, and to assess the protective effect of a new synthetic protease inhibitor, E3123 (2-guanidinobenzoate methane sulphonate).

Pancreatic injury was induced by short-term (4 h) pancreaticobiliary duct obstruction (PBDO) with secretin infusion ($0.2 \text{ units kg}^{-1} \text{ h}^{-1}$). *In vitro* leakage of malate dehydrogenase (MDH) and cathepsin B (CAT) from pancreatic lysosomes and mitochondria, and pancreatic adenylate energy change (EC) levels were assessed.

PBDO with secretin infusion caused significant rises in portal serum amylase (mean(s.e.m.) $31(4)$ versus $6(1) \text{ units ml}^{-1}$ in controls), CAT levels ($7.5(0.7)$ versus $2.6(0.3)$ in controls), pancreatic water content ($86(3)$ versus $74(2)$ per cent in controls), and congestion of amylase ($384(27)$ versus $257(21) \text{ units mg DNA}^{-1}$).

This treatment also caused an accelerated leakage of both CAT and MDH from lysosomes and mitochondria, as well as impaired EC levels (0.7(0.06) *versus* 0.95(0.03) in controls). These changes had almost disappeared 24 h after removal of PBDO. The administration of E3123 at 5 mg kg⁻¹ h⁻¹ during PBDO almost completely prevented these changes, while a dose of 2 mg kg⁻¹ h⁻¹ showed a partial protective effect.

These results suggest that increased subcellular organelle fragility and impaired pancreatic energy metabolism play an important role in the pathogenesis of pancreatic injury induced by PBDO with intraductal hypertension. A low molecular weight protease inhibitor such as E3123 may be clinically useful in the treatment of gallstone pancreatitis, which is usually accompanied by obstruction of the pancreatic or biliary ducts, or both.

Mortality and morbidity rates of pancreatic injury

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Using the organ injury scale (OIS)¹, we have reviewed the morbidity and mortality rates of 24 patients with pancreatic injuries confirmed after laparotomy from 1973 to December 1991.

Seventeen patients (mean age 29 years) survived (group A) and seven (mean age 50 years) died (group B). The severity of injuries were: three grade I (one died), four grade II, 11 grade III (three died), three grade IV and three grade V (all died). Shock was present in seven cases of group A and in five of group B; 11 patients in group A sustained an emergency operation and six were delayed because of underestimation of the extent of injury; in group B only one patient had a delayed operation; duodenal lesions were more severe in this group.

No death in group B could be related to the pancreatic trauma itself, but rather to the severity and complications of the trauma.

Early pancreatic complications were five pseudocysts, two pancreatic fistulae and four cases of acute pancreatitis; late complications were one pseudocyst and one acute pancreatitis. Delayed diagnosis and treatment of pancreatic lesions caused more complications which needed operative treatment (four of the five pseudocysts and both fistulae).

In conclusion, early survival of patients sustaining pancreatic trauma correlates with age, shock and associated injuries; the pancreatic morbidity rate is reduced by early recognition of the pancreatic lesion and choice of treatment. The OIS is useful for selecting the most suitable treatment but it is not a predictive factor for mortality or morbidity rates.

1. Moore EE, Cogbill TH, Malangoni MA *et al.* Organ injury scaling. II. Pancreas, duodenum, small bowel, colon, and rectum. *J Trauma* 1990; **30**: 1427-9.

Place for 'split' pancreaticojejunostomy in the surgical treatment of chronic pancreatitis

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In 1967, James described an operation for the treatment of chronic pancreatitis (CP) which he called 'split' pancreaticojejunostomy (PJ). This procedure consists of a vertical, partial transection of the pancreas with a double anastomosis of the sectioned pancreatic duct to a Roux-en-Y limb of jejunum.

In this study a modified version of this method was used for the treatment of CP in which the main pancreatic duct appeared to have a normal calibre. The long-term results of this method in eight patients (four alcoholic CP, three familial CP, one idiopathic CP) are reported. Endoscopic retrograde cholangiopancreatography (ERCP) in these patients showed irregular, but non-dilated, main pancreatic ducts, precluding the use of a lateral, side-to-side PJ. The pancreas was totally transected in the region of the corpus allowing prompt identification of the sectioned pancreatic duct. Both sides of the duct were anastomosed face to face, to a Roux-en-Y jejunal limb using a mucosa-to-mucosa technique. Double, transanastomotic silicon stents were left for 10 days.

Postoperative complications consisted of intra-abdominal abscess (one case) and sepsis/acute respiratory distress syndrome (one case,

in conjunction with a simultaneous cystoduodenostomy). Follow-up was 20-50 months. Clinical outcome was rated good, fair, or bad, according to relief of pain. Five of the eight patients had a long-lasting improvement of symptoms (four good, one fair, three bad). From these results it is concluded that 'split' PJ is a valid alternative for the treatment of CP when a conventional lateral PJ is not feasible.

Characterization of the extracellular matrix in the normal and diseased human pancreas

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The connective tissue content and composition of the normal pancreas changes markedly in pancreatic disease. The aim of the present study was therefore to characterize the different components of the collagenous and elastic fibre systems in normal human pancreas as well as in chronic pancreatitis (CP) and pancreatic carcinoma (PC) by use of transmission and scanning electron microscopy and immunohistochemical methods in fresh pancreatic tissue.

The localization of type III, IV, VI and VII collagen was detected using monoclonal antibodies on 8-µm sections.

In the normal pancreas the diameters of the collagen fibrils ranged from 20 to 130 nm (distribution peak 60 nm). In CP an increase in the range of fibril diameters (20-210 nm; peaks 30 and 100 nm) was observed and even more so in PC (20-390 nm; peak 30 nm). In morphometrical studies the matrix density of collagen fibrils was 1232-1890 fibrils mm⁻² in normal pancreas, 590-18768 fibrils mm⁻² in CP, and 3980-55640 fibrils mm⁻² in PC. Detection of collagen types by use of monoclonal antibodies showed in normal pancreas type III collagen localized predominantly in septa, periductally and perivascularly. Type IV collagen depositions were found along the basal membrane. Branching type VI collagen was a minor constituent of the normal extracellular matrix with thin fibrillar structures showing a slight waving course. In CP, type III collagen was markedly enhanced, while type IV tetramers and type VI fibrils were reduced. In PC samples, type IV collagen was drastically diminished, but type III and VI fibrils were more frequently found. Neither in normal pancreas nor in CP and PC tissue was type VII collagen detectable. The distribution of elastic connective tissue components in normal pancreas was 19 per cent oxytalan, 5 per cent elaunin and 76 per cent mature fibres. A shift from mature to more immature precursor elastic fibres was observed in CP (oxytalan 27 per cent, elaunin 6 per cent, mature fibres 67 per cent) and was even more pronounced in PC (oxytalan 39 per cent, elaunin 8 per cent, mature fibres 53 per cent).

In conclusion, this study describes marked extracellular matrix changes in CP and PC compared with the normal pancreas.

Acute biliary pancreatitis: a prospective therapeutic study

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Ninety patients suffering from acute biliary pancreatitis were prospectively studied in the past 4 years. The diagnosis and classification were done according to our own system with non-morphological parameters to obtain an index of severity, and confirmed by ultrasonographic methods, laparotomy and/or cytology. There were 25 mild, 54 moderate and 11 severe cases. Immediate medical treatment was commenced and surgical treatment of the biliary pathology was performed on the sixth to eighth day. Patients were not operated on before 48 h after admission, except those with severe pain, jaundice or local complications; 75 patients (83 per cent) were operated on. The gallbladder was removed in all patients with cholelithiasis (97 per cent). Choledocholithiasis was found in 34 per cent of patients. Direct or indirect papillary operations were performed in 16 and 12 per cent respectively. Four patients underwent endoscopic treatment only. Pancreatic necrectomy was performed in 4 per cent. The postoperative morbidity rate was 9 per cent (seven of 75). There were no deaths in mild and moderate cases whereas the mortality rate in severe cases was 9 per cent (one of 11). The overall mortality rate was 1 per cent with one death in 90 patients.

Isolated portal vein thrombosis: an exceptional complication of chronic pancreatitis

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While splenic vein thrombosis is a well described feature of chronic pancreatitis, obstruction of the superior mesenteric and/or portal veins is less well known. Only 25 cases have been reported in the literature up until 1990.

We report a case of portal vein thrombosis in a 42-year-old man with no history of chronic alcohol abuse, who presented with intense abdominal pain. On endoscopic ultrasonography and computed tomography (CT) a cavernous transformation of the portal vein and a suspect tumoral area in the pancreatic isthmus were observed. No

oesophagogastric varices were detected by endoscopy. Diagnosis of isolated portal vein thrombosis without splenic vein thrombosis was confirmed by dynamic CT and coeliac angiography. Because a pancreatic cancer was suspected a subtotal pancreatectomy was performed, preserving the spleen and the cavernous transformation of periportal collaterals; this permitted a histopathological diagnosis of chronic pancreatitis. The postoperative course was uneventful and the patient became pain-free.

Only nine cases of the 25 cases of central venous obstruction reported in the literature showed an isolated portal vein thrombosis without splenic vein thrombosis. Generally, in the absence of endoscopic oesophagogastric varices (two of three cases) a prophylactic portosystemic decompression seems entirely unnecessary because the risk of bleeding is very small. When a curable pancreatic cancer is suspected, we think that it is possible to resect the pancreas, preserving the spleen and periportal varices and enabling a histological examination.

Peptic ulcer

Prophylaxis of stress ulcers: comparison between ranitidine and sucralfate in surgical patients in intensive care

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A prospective randomized study was designed to investigate whether different methods of ulcer prophylaxis result in various incidences of nosocomial pneumonia in surgical patients in intensive care.

Patients included those receiving ventilation after severe multiple trauma (injury severity score > 25), those with brain trauma (grades II and III), sepsis, haemorrhagic shock, undergoing operations with more than ten transfusions, with liver and respiratory insufficiency but without current ulcer therapy or earlier stomach operations. Patients were randomly allocated to three groups: (1) ranitidine (200 mg 24 h⁻¹) with subglottic lavage; (2) sucralfate (6 × 1 g 24 h⁻¹) with subglottic lavage; and (3) sucralfate (6 × 1 g 24 h⁻¹) without subglottic lavage.

The mean duration of treatment was 10 (range 3–38) days. Stomach acidity was measured six times daily. Samples for culture were taken daily from blood, stomach, mouth and trachea. The outcome criteria were rebleeding (endoscopically confirmed) and pneumonia.

In this interim study, 65 patients (group 1, 23; group 2, 20; group 3, 22) could be analysed, consisting of 35 patients with multiple trauma, 13 with brain trauma, nine with respiratory insufficiency, and eight others. Seventeen patients died during the first 4 weeks (group 1, six; group 2, four; group 3, seven) as a result of the effects of injury or organ failure. In group 2 there were two cases of pneumonia; one in group 3; and none in group 1. Two bleeding episodes were seen in group 1, and none in groups 2 or 3. Pneumonia appeared to occur only in patients with lung contusion or lung bleeding, although there were no differences in the micro-organisms grown from the stomach and trachea.

Sucralfate has at least the same efficiency as H₂ blockers with fewer side-effects and lower costs of treatment, and the protection of the stomach mucosa is excellent. Sucralfate is suitable for prophylaxis of stress ulcers in surgical patients in intensive care.

Induction of haemorrhagic lesions in the stomach by intravenous injection of aspirin, salicylate and dipyridamole

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Orally ingested acetylsalicylic acid is able to induce haemorrhagic lesions in the stomach in the presence of acid. Since the drug is also a powerful blocker of thrombocyte aggregation, we examined its role in the induction of gastric lesions.

Male rats were subjected to urethane anaesthesia and the trachea, oesophagus, carotid artery and jugular vein were cannulated. After a basal phase the stomach was perfused with 150 mmol l⁻¹ HCl at 4 ml h⁻¹. Controls received saline. Each group of eight to ten animals received either aspirin (ASS) (100 mg kg⁻¹), sodium salicylate (SAL) (100 mg kg⁻¹), dipyridamole (DIP) (5 mg kg⁻¹) or saline. Blood gas readings and pH values were recorded. After 3 h the stomachs were fixed in formalin and cut along the greater and lesser curvature. The lesions were counted planimetrically and subjected to statistical analysis.

With intragastric HCl, 5 mg kg⁻¹ DIP induced a mean (s.d.) lesion area of 26(0.6) mm², 100 mg kg⁻¹ ASS induced 12.4(0.4) mm², 100 mg kg⁻¹ SAL induced 4.9(1.7) mm² and saline 4.6(1.4) mm². The results were significantly different.

Intravenous ASS induces gastric lesions in the presence of intragastric acid, whereas SAL is no different from controls. The most powerful inducer of gastric lesions was dipyridamole. Thus, the inhibition of thrombocyte aggregation by aspirin may be partly responsible for its induction of haemorrhagic lesions.

Injection sclerotherapy in bleeding duodenal ulcer

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We present the results of injection sclerotherapy in 63 patients bleeding from duodenal ulcers. Forty-two patients were bleeding during endoscopy (Forrest I) and in 21 patients the stigmata of recent bleeding (visible vessel or adherent clot to the ulcer base) were observed (Forrest II). Peptic ulcer was diagnosed in 56 patients and stress ulcer in seven. Initial haemostasis was achieved in 93 per cent of patients with Forrest I. In three cases, injection sclerotherapy proved to be unsuccessful and an emergency surgical procedure had to be performed: in two cases, the ulcer was located on the posterior wall of the duodenal bulb and in the third case it was impossible to pass a stenotic pylorus to inject the bleeding lesion. Recurrent bleeding occurred in five (12 per cent) patients with Forrest I and in two (10 per cent) patients with Forrest II. In three cases injection sclerotherapy was successfully repeated and four patients with recurrent bleeding underwent surgery. Final haemostasis was achieved in 89 per cent. In peptic ulcer cases, injection sclerotherapy proved to be successful in 87 per cent, and in stress ulcer haemostasis was achieved in all the patients.

Injection sclerotherapy is a simple, safe and effective method of stemming bleeding from duodenal bulb ulceration, avoiding the need for emergency operation in the majority of cases.

Severe upper gastrointestinal bleeding due to peptic ulcer

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Despite improvements in exploratory methods and the introduction of endoscopic haemostasis procedures, bleeding remains a severe complication of peptic ulcer. A retrospective study of 186 cases collected over a 2-year period showed an overall mortality rate of 11.2 per cent: 8.8 per cent in non-surgical patients and 13.6 per cent in patients undergoing surgery, but only 7 per cent when patients with cirrhosis were excluded. The criteria required for surgical treatment and the choice of the most appropriate operative technique are defined. In elderly people and/or in patients with underlying disease, when the blood pressure is stable, surgical risk is less than the risk of cardiovascular collapse. This type of surgery is justified only if it eliminates all risk of recurrent bleeding.

Surgical treatment of perforated peptic ulcer: simple closure versus a definitive technique

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This is a retrospective study of 285 patients undergoing operation during a 19-year period for perforated peptic ulcers. There were 259 men (91 per cent) and 26 women. During the period studied there was a marked decrease in the incidence of perforated peptic ulcer.

Simple closure was performed in 68 per cent of patients, but tended to be performed less frequently in the later years, when definitive surgical procedures became more frequent.

Plain abdominal radiography showed a pneumoperitoneum in 80 per cent of cases. The most frequent site of perforation was the duodenum, followed by the pylorus. Purulent peritonitis was found in 35 per cent of patients. The overall mortality rate was 7 per cent, with no significant difference between the two types of operative procedure.

Visick grading showed better results after definitive surgery. We conclude that a definitive surgical technique should be performed in almost all patients with perforated peptic ulcer. Simple closure should be performed in the presence of purulent peritonitis or when there is a duodenal or pyloric ulcer with a history of < 3 months. All other cases require definitive surgery.

Risk factors associated with surgical treatment of perforated peptic ulcer

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The aim of this study was to evaluate the risk factors and the results of treatment for perforated peptic ulcer, to compare them during different periods of the study, and to determine the current optimal surgical treatment.

In a retrospective study, the case records of all patients admitted with a diagnosis of perforated peptic ulcer between January 1976 and October 1991 were reviewed. The features believed to be of importance in the outcome were first assessed by univariate analysis. Those found to be significant were then included in a multivariate study. Lastly, a comparison was made between three periods of the study (1976–1980, 1981–1985, 1986–1990).

In all, 247 patients were included, of whom 29 (11.7 per cent) died. Factors associated with an increased mortality rate were shock on admission ($P = 0.01$), age ($P < 0.001$), severe associated medical illnesses ($P < 0.001$) and the form of treatment ($P < 0.01$). Multivariate analysis excluded age from the risk factors. Chronic peptic ulcer disease occurred in 188 of 247 (76.1 per cent) of the patients. Comparison of the different periods studied showed that age, associated illnesses, percentage of acute or subacute ulcers, mortality rate and overall number of patients are all increasing.

The main determinant of surgical treatment for perforated ulcer is the patient and his or her general state. Because of the high frequency of chronic peptic ulcer disease, I believe that the 'gold standard' in the treatment of perforated peptic ulcer remains definitive surgery. However, in the presence of more than one risk factor, simple suture and patch are probably safer. In view of the increasing frequency of perforation, one wonders if the indications for definitive surgery should be broadened before complications occur.

Omeprazole versus ranitidine and somatostatin in the treatment of acute severe gastroduodenal haemorrhage

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Peptic ulcer pathology is the most common cause of upper gastrointestinal bleeding. Omeprazole has recently been introduced for treatment of duodenal and gastric ulcers. A randomized controlled clinical study was performed to investigate the efficacy of intravenous omeprazole in the treatment of acute gastroduodenal peptic bleeding in comparison with a standard medical approach (H_2 antagonist plus somatostatin).

A prospective randomized trial was carried out in 30 patients over 12 months. All consecutive patients admitted with severe upper gastrointestinal bleeding and some degree of clinical shock were considered eligible; they were resuscitated and underwent emergency endoscopy. Only patients affected by gastric or duodenal peptic ulcer or haemorrhagic gastritis were included in the study. Twenty patients fulfilled these criteria and were randomly allocated to one of the following treatment schedules: (1) omeprazole 80 mg bolus intravenously (i.v.) followed by continuous infusion of 8 mg h^{-1} for 12 h and then 4 mg h^{-1} until clinical stabilization was achieved. This was followed by 40 mg by mouth until endoscopic healing; (2) somatostatin $250 \mu\text{g}$ i.v. bolus followed by continuous infusion of $250 \mu\text{g h}^{-1}$ and ranitidine 50 mg i.v. every 4 h until clinical stabilization. No antacids or other ulcer-related medications were allowed during the study period. Gastric lavage was not performed through the nasogastric tube. The two groups of patients were well matched for sex, age, source of bleeding and basal laboratory and clinical parameters.

Mean transfusion requirements until stabilization were similar in both groups (1570 ml omeprazole versus 1600 ml ranitidine plus somatostatin). Mean (s.d.) time for cessation of bleeding and clinical stabilization was 2.63 (0.75) days in the omeprazole (O) group, 2.83 (1.35) days in the ranitidine plus somatostatin (R + S) group. During the initial 48 h of treatment 15 patients stopped bleeding. In five patients (three in R + S, two in O group) bleeding did not stop, but decreased in intensity as established by the reduced need for transfusion and by examination of gastric aspirate. In these patients treatment was continued for another 48 h and only one patient (R + S group) required emergency surgery 4 days after beginning treatment. Thus a total of 14 patients stopped bleeding after 48 h of treatment (80 per cent O versus 70 per cent R + S group) and 95 per cent

stopped bleeding after 96 h of treatment (100 per cent O versus 90 per cent R + S group). No biochemical changes observed during treatment could be attributed to either drug and there were no side-effects apart from the almost total inhibition of gastric secretion with omeprazole.

In conclusion, omeprazole showed a therapeutic efficacy similar to that of a combination of ranitidine and somatostatin in control of gastrointestinal bleeding.

Anterior lesser curve seromyotomy with posterior truncal vagotomy

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For the past 10 years we have used anterior lesser curve seromyotomy with posterior truncal vagotomy (ASPTV) as the operation of choice for chronic duodenal ulcers. This study is a prospective evaluation of morbidity and mortality of 137 patients operated on between December 1982 and November 1991.

There were 111 men and 26 women, mean age 39 years. The first 128 patients were operated on by laparotomy and the last nine at laparoscopy. All patients had endoscopic follow-up.

There was no mortality and no abdominal wound dehiscence. Perioperative haemorrhage was not encountered and no splenectomies were done. In the laparotomy group, there were two patients with each of the following complications: postoperative perforation (1.5 per cent), pulmonary infection (1.5 per cent) and wound infection (1.5 per cent), and one patient each developed a prolonged ileus and early dysphagia (0.7 per cent). After laparoscopy, the only complication was postoperative perforation which occurred in two cases (22 per cent).

Late postoperative results were assessed in 102 patients more than 6 months after surgery. The mean duration of follow-up was 50 months. Sixteen patients had been lost to follow-up. There was one (1 per cent) incisional hernia. There were no cases of dumping syndrome. There were eight (8 per cent) recurrent ulcers.

In conclusion, the results of ASPTV after laparotomy or laparoscopy are similar to those seen after highly selective vagotomy. We prefer this present technique which is simple and rapidly performed.

Minimal linear gastrectomy: a new experimental method to denervate the anterior gastric wall

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The aim of the study was to compare the levels of gastric acidity after posterior truncal vagotomy (PTV) and seromyotomy with those after PTV and minimal linear gastrectomy (MLG).

Gastric pH was measured weekly in 31 Wistar rats for 3 months after operation. They were divided into four groups. Group I (control) underwent PTV; group II had seromyotomy and PTV; group III had MLG using a TA stapler (US Surgical, Norwalk, USA) and PTV; and group IV had MLG with a GIA stapler (US Surgical) and PTV.

The basal pH measurements are shown in the Table.

	Before surgery (n=31)	Group I (n=7)	Group II (n=8)	Group III (n=8)	Group IV* (n=8)
Mean (s.e.m.)	2.86 (0.10)	3.73 (0.64)	4.71 (0.69)	5.02 (0.65)	5.33 (0.60)
Maximum	4.85	4.34	5.60	5.65	6.21
Minimum	2.18	2.94	3.76	3.85	4.95
Coefficient of variation (%)	0.20	0.21	0.21	0.18	0.16

* $P < 0.05$ versus other groups

MLG and PTV resulted in a greater reduction of basal gastric pH than seromyotomy with PTV.

Intragastric 24-h pH monitoring before and after highly selective vagotomy

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Highly selective vagotomy (HSV) is known to inhibit acid secretion by 40–50 per cent. Using preoperative and postoperative intragastric pH monitoring this study attempted to estimate the individual benefit of vagotomy in patients with refractory ulcers and to correlate pain and ulcer recurrence with the acid secretory pattern.

In 25 patients (23 men, two women; mean(s.d.) age 45(12) years) intragastric 24-h pH monitoring was carried out before and after HSV performed for refractory duodenal ulcers of 6–10 years' duration. After 3 years 13 of the patients had recurrence of pain and ulcer symptoms; ulcer recurrence could be proven by endoscopy in six cases. The pH probe was placed under fluoroscopic control into the antrum and pH values were registered from pH 1–7 in ambulatory patients eating regular meals three times a day. In order to demonstrate a relation between alkaline pH and acid secretion, differences between time at pH 1–2, pH 2–3, pH 3–4 and pH > 4, and total time were calculated.

There was a significantly higher pH of longer duration in patients with recurrence of ulcer symptoms also showing stronger acid inhibition. Acid reduction is effective in both groups, but more pronounced in the 'recurrences'.

Duodenogastric alkaline reflux is known to increase antral pH above 4 and therefore can be detected by 24-h pH monitoring. Results of this study suggest that in patients after HSV the alkaline milieu in the antrum caused by reflux may be partly responsible for the recurrence of ulcer symptoms and ulcers.

Protective effect of drugs improving mucosal blood flow on morphological injuries induced by ethanol

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It is well known that absolute ethanol given intragastrically induces severe mucosal damage in the rat stomach. The purpose of the present study was to evaluate the effect of pretreatment with drugs which enhance mucosal blood flow on the severity of alcohol-induced gastric injuries.

Sixty-two Wistar rats were divided into two groups. Animals of group A ($n = 42$) were assigned to eight subgroups. Absolute ethanol (0.8 ml per 100 g body-weight) was given to all but one subgroup through an orogastric tube. In subgroups I ($n = 6$) and II ($n = 12$) normal saline (0.8 ml per 100 g) and ethanol was given respectively. In animals of all remaining subgroups, 30 min before ethanol instillation the following drugs were given by mouth: subgroup III ($n = 6$), isoprenaline (5 µg per 100 g); IV ($n = 6$), isoprenaline (10 µg per 100 g); V ($n = 6$), nifedipine (0.07 mg per 100 g); VI ($n = 6$), nifedipine (0.14 mg per 100 g); VII ($n = 6$), dihydralazine (0.03 mg per 100 g); VIII ($n = 6$), isosorbide (0.03 mg per 100 g). The animals were killed 1 h after ethanol administration and the stomach removed, opened along the greater curvature and photographed. The area of gross mucosal lesions was determined by planimetry and expressed as a percentage of the total surface. The mean(s.d.) percentage area of damage in the different subgroups was: I, 0 per cent; II, 44.37(5.59) per cent; III, 12.18(4.64) per cent; IV, 2.70(1.05) per cent; V, 8.72(3.49) per cent; VI, 2.92(0.85) per cent; VII, 2.44(0.85) per cent; VIII, 2.30(0.69) per cent. Values from all subgroups were statistically significant when compared with those of subgroup II.

In group B ($n = 20$) animals were treated with the same protocol and ethanol blood levels were determined, with no significant difference noticed between subgroups.

This study shows that orogastric instillation of absolute ethanol in rats resulted in severe mucosal damage. Pretreatment of animals with drugs increasing mucosal blood flow seems to protect gastric mucosa from ethanol injuries.

Risk factors affecting mortality rate in acute gastric mucosal lesions

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There is still a significant mortality rate in patients with acute gastric mucosal lesions. Records of 45 patients with such lesions operated on in a 14-year period (1976–1990) were retrospectively analysed to assess the factors affecting the mortality rate.

The operative mortality rate was 38 per cent. Univariate and multivariate analyses were employed to demonstrate if any of the previously derived set of clinical variables were related to the operative mortality rate. The clinical variables used were age, sex, indication for hospitalization, hypotension, recent operation, drug administration, transfusion, recent upper gastrointestinal bleeding, concurrent major medical illness, concurrent sepsis, medical therapy, type of operation, postoperative complication, rebleeding, and reoperation for mucosal lesions.

Major medical illness ($P < 0.001$), postoperative complication ($P < 0.001$), rebleeding ($P < 0.02$) and reoperation ($P < 0.04$) were found to affect the prognosis according to univariate analysis. Only postoperative complication ($P = 0.0150$) and concurrent major medical illness ($P = 0.0182$) were significant factors affecting the mortality rate with coefficient values of 6.496 and 4.646, respectively, when multivariate analysis was performed.

In conclusion postoperative complications and major medical illness are the most significant variables affecting the mortality rate of acute gastric mucosal lesions. Age, sex, indication for hospitalization, hypotension, recent operation, recent upper gastrointestinal bleeding, drug administration, amount of transfusion, sepsis, type of operation and rebleeding after the first operation are not found to alter the prognosis.

Effects of truncal vagotomy on gastric mucosal mast cells

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This study was designed to look at mucosal mast cells (MMC) and the distribution and degranulation of the secretory portion of the rat stomach under basal conditions, and to assess the changes induced following truncal vagotomy (TV).

A total of 60 male Wistar rats was allocated to six groups of ten, the first group serving as control. The second group received simple pyloroplasty (P) and were killed at 60 days. TV–P were performed in the animals of the other four groups and they were killed at 30, 60, 90 and 120 days after the surgical procedure. The histological study of MMC including cell count and degranulation appearance, was carried out in 4-µm sections of the gastric mucosal layer and toluidine blue was used for staining.

The distribution of MMC is shown in the Table. There was a gradual decrease in MMC population after TV. The degranulation pattern of MMC by TV–P is also shown, and demonstrates an increased percentage of degranulated MMC with time after TV–P.

	MMC (number mm ⁻²)	MMC degranulation (%)
Control	307.4(30)	18.8(3)
P 60 days	282.7(27)	16.6(2)
TV 30 days	312.7(37)	19.1(3)
TV–P 60 days	205.7(33)*	26.9(6)*
TV–P 90 days	156.4(18)*	36.1(3)*
TV–P 120 days	145.3(39)*	40.8(8)*

Values are mean(s.e.m.). * $P < 0.05$ versus control group

The gradual decrease in MMC population after TV–P is striking. The number of degranulated cells remained constant and the percentage of degranulated cells gradually increased. This suggests that the vagus not only acts on mast cell degranulation but also exerts trophic control over these cells.

Experimental study of vagal regeneration on the anterior gastric wall: seromyotomy *versus* gastrotomy and suture

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The purpose of this study was to compare neural regeneration on the anterior gastric wall after seromyotomy with that which occurs after gastrotomy from the antrum to the fundus.

A study was made of 28 Wistar rats. There were three groups: control (C) – laparotomy and reference stitch on the anterior gastric wall (eight animals); seromyotomy (S) of the gastric corpus and fundus and truncal posterior vagotomy (TPV) (ten animals); and gastrotomy (G) of the gastric corpus and fundus with suture and TPV (ten animals).

Neural regeneration was studied 2 months after operation using immunohistological techniques.

Groups S and G had gastric dilatation on post-mortem examination. Both showed complete denervation of the anterior gastric wall (absence of vagal fibres crossing the resection line) although the presence of amputation neuromas and Schwann cells was frequently found.

Both seromyotomy and gastrotomy with suture are efficient methods for denervating the anterior wall of the stomach.

Pepsinogen assay in postoperative gastric pathology

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Pepsinogen I is a gastric enzyme produced in the oxyntic glands of the stomach. Its serum levels may be used as markers of the physiological status of the stomach after surgery.

Thirty-five patients divided into two groups were studied. The first was composed of 21 patients who had had a gastrectomy (mean age 51 years), and the second group included 14 patients who had had a vagotomy (mean age 44 years). In both groups, pepsinogen I blood determinations and endoscopy were performed. In group 1 a gastric biopsy was also performed.

In group 1, all biopsy samples showed chronic gastritis, with severity varying from superficial gastritis (27 per cent) to atrophic gastritis (73 per cent). The higher levels of pepsinogen I are related to superficial gastritis and the lower levels to atrophic gastritis. In group 2, pepsinogen I was increased compared with a control group (mean(s.e.m.) control $113.6(8.5) \text{ ng ml}^{-1}$ *versus* $156(18) \text{ ng ml}^{-1}$ in patients). The elevation was higher in patients with endoscopic recurrence of the ulcer.

Higher levels of pepsinogen I were found to be related to superficial gastritis in patients undergoing gastrectomy. Also, higher levels of pepsinogen I were noted in patients undergoing vagotomy with recurrence of the ulcer.

Clinical course and surgical treatment of the cutaneous blue naevus

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Little is known of the natural history of the blue naevus. This tumour is a cellular naevus with an unknown malignant potential.

From 1949 to 1989, 105 patients underwent excision of blue naevi. There were 81 women and 24 men; the median age at excision was 37 (range 6–84) years. The patients' attention was drawn to the tumour because of growth in diameter, change of colour or itching. The majority of tumours were located on the head and neck (36 cases), followed by the extremities (lower 28, upper 23). Median tumour diameter was 6 (range 1–100) mm. Excision was performed with a margin of 5 (range 1–50) mm, including subcutis. Defects were mainly closed directly (83 cases). The most frequent tumour was the common blue naevus (77), followed by the cellular blue naevus (18) and the malignant blue naevus (ten). None of the common blue naevi recurred but three of the cellular ones did, two local and one regional. Furthermore, three malignant blue naevi recurred locally; one of these also recurred regionally and another one also distally.

In conclusion, clinical follow-up of patients after excision of common blue naevi seems unnecessary. Both the cellular and the rare malignant variety may recur and these patients must be followed clinically. Clinically, it is not possible to differentiate between the three types.

Mandibular reconstruction by free composite peroneal flaps

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The microvascular transfer of osseocutaneous flaps now allows state-of-the-art reconstruction of many of the difficult bony and soft tissue defects in mandibular surgery.

We have operated on nine patients (five women, four men) for cancer of the mandible. In eight cases the tumour was a cancer of the floor of the mouth which encroached upon the mandible. One osteosarcoma of the mandible was treated. The reconstruction was performed with a vascularized and innervated osteoseptocutaneous free fibula flap. In eight of the nine patients osteotomies were performed.

No postoperative death was observed and no failure of the graft occurred. In one case the reconstruction plate was removed because of local infection. Bone healing occurred by the end of the third month. We have monitored this transplantation by clinical examination, radiography, bone scan and Doppler measurements. The patients recovered their proprioceptive sensitivity by the fifth postoperative month.

In conclusion, the vascularized and innervated peroneal free composite flap is now the most elaborate technique for mandibular reconstruction. The indications for this flap include mandibular bone damage greater than 7 cm, tissue loss in the mandibular region, irradiated or poorly vascularized tissue and mandibular injury.

Use of the omentum in chest wall reconstruction after removal of primary breast cancer

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This chest wall reconstruction procedure is suggested after removal of locally advanced breast cancer. In October 1989, a 51-year-old patient presented with an ulcerated breast cancer destroying the chest wall. Bone scintigraphy showed scattered bone metastases. The patient underwent chemotherapy and hormone treatment; after 2 months a partial sternum removal along with surgical cleaning of the ulcer became necessary. Five months later the patient underwent hysterectomy and oophorectomy followed by chest wall reconstruction with omentum and immediate skin grafts. Two years later the

patient is well; there is an actual reduction of the bone metastases and the associated paraneoplastic syndrome (piastrinaemia) has disappeared. This application of omentum to chest wall reconstruction has not been previously documented, apart from the repair of serious osteoradionecrotic injuries or after removal of local mammary tumour recurrence. A marked improvement in the patient's quality of life along with good oncological results have been obtained, with the aid of hormone treatment and chemotherapy. It is possible that the omentum could have modulated a local immune reaction. The omentoplasty technique for chest wall reconstruction should be borne in mind by the surgeon.

β -Interferon in the control of pathological skin scars

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The results of a clinical and laboratory study on the efficacy of β -interferon in the control of wound healing are presented.

In the laboratory, fibroblasts from keloids were put in contact with β -interferon in order to evaluate its antiproliferative activity. In the clinical trial, 40 patients who had undergone various surgical operations producing wounds presenting a risk of keloid scars were treated by the local application of β -interferon ointment (5 g day^{-1}) from the seventh day after the operation to at least the 67th postoperative day. This group was compared with an equivalent untreated control group. The trial took place over 2 years.

In addition to the antiproliferative activity of β -interferon, laboratory results have given evidence of a clear inhibition of collagen production. The clinical trial demonstrated a significant difference in the onset of pathological healing between the two groups.

These preliminary results suggest a possible role for β -interferon in the treatment of keloids and in the prevention of their relapse after surgical excision.

New concepts in the study of tissue vascularization. I. The fractal approach

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There are several methods of quantifying the vascularization of tissues: the principal method is the determination of the density of vessels (number of vessels or their total length by microscopic field observed). Fractal analysis is an original and objective method that has been used for the first time in the study of skin vascularization. It has been used very extensively in physics, geography and economics. However, to our knowledge, its previous medical applications have been only to cardiology (electrocardiography), neurology (electroencephalography), ophthalmology, and cardiopulmonary physiology.

Two-dimensional image analysis of vascular networks has been carried out. Fractal analysis of similar structures relies on the fact that different box sizes used to cover vessel structure will yield different estimates of vessel length. This relation is given by: $N(\delta) = k^{-D}$, where D is the fractal dimension, δ is the box size, and $N(\delta)$ is the number of boxes needed to cover the structure of the vessels studied. D is determined from the slope of the plot ($\log \delta$, $\log N(\delta)$). D lies between 1 and 2; the closer D is to 2, the more complex and ramified the structure, so that the fractal dimension is a measure of the ability of a vascular network to irrigate the skin area studied.

In our investigations the aortas of mice were injected with Indian ink. The skin of the posterior aspect of the thigh, which is supplied by cutaneous branches that arise from muscular arteries, was analysed. Photographs were taken and analysed as above.

Our results demonstrated that skin vascular networks possess a fractal structure; theoretical and practical aspects of fractal analysis are discussed, as well as clinical perspectives.

New concepts in the study of tissue vascularization. II. A mathematical model of skin vascularization

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Fractal analysis of axial-perforator and arteriovenous vascular trees was performed on the skin of mice after injection of the arterial network by Indian ink. Fractal analysis was performed by box-counting. Fractal dimension (D) was determined for 35 venous and 31 arterial perforator vessels (D 1.302 and 1.264, respectively), and five venous and three arterial axial vessels (D 1.374 and 1.328, respectively) ($r^2 \geq 0.985$). All vascular networks show a fractal structure, characterized by a specific D . These values are relatively constant; D is a function of the anatomical and physiological characteristics. There was no significant difference between venous and arterial networks, nor was there between axial and perforator networks ($P < 0.05$); this demonstrates a similar efficacy in terms of perfusion of the skin.

A computer simulation based on fractal theory has been developed to reproduce the two kinds of vascular networks. Fractal theory is based on the principle of self-similarity, which is to say that a fractal is a shape made of parts similar to the whole. Fractals are the result of a construction procedure that is repeated and repeated, so that the iteration of a very simple rule can produce seemingly complex shapes, such as vascular networks. The basic module that is repeated in the whole structure is Y shaped and is termed the generator; this generator is applied to a basic structure, called the initiator. After a few iterations, a vascular network is obtained. The difference between axial and perforator vascular networks is the choice of the initiator, whereas the generator is identical. The growth of the two kinds of perfusions appears in the same tissue environment; there is no reason why, in the same tissue, for an identical physiological function, there should be a difference in the growing pattern of these vessels. Only the origin of these blood vessels is different, and this is taken into account by the model, in having different initiators; this explains the difference in macroscopic aspects. Finally, several variables of this mathematical model are discussed.

Surgical treatment of doxorubicin and epirubicin extravasation guided by fluorescence microscopic analysis

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Extravasation of doxorubicin or epirubicin leads to severe progressive necrosis. The treatment is early excision of all affected tissue. Using fluorescence microscopy it is possible to demonstrate and delineate extravasation of these two drugs.

From 1987 to 1991, 24 patients (six men, 18 women) with a median (range) age of 56 (10–78) years were admitted to our department with suspected extravasation of doxorubicin or epirubicin. Fluorescence microscopic analysis of frozen sections was used to assess whether extravasation had taken place. Nine patients had fluorescence-negative specimens and were observed without subsequent development of necrosis. Fifteen patients had fluorescence-positive specimens and the affected area was excised with a free margin of 1 cm in all directions if possible (median size of defect 11 (range 6–30) cm). The defects were covered with split skin grafts. Four patients developed further necrosis which required operation. The prognosis according to later sequelae, such as impaired function of affected extremity, was related to delay (i.e. time from injury to surgery) and to the anatomical region chosen as the infusion site. Poorest results were seen if more than 6 h had elapsed since the injury, or if the cubital fossa or the hand was chosen for infusion. Nine patients developed sequelae.

To avoid extravasation of such potent cytostatics and to limit the sequelae after accidental extravasation, it is important to choose a safe infusion site, to use the right equipment for infusion, to observe the patient (infusion site) carefully and to act promptly if extravasation is suspected. Fluorescence microscopic analysis of frozen sections is found to be a reliable and easy method of detecting and delineating doxorubicin and epirubicin extravasation.

Multiple symmetrical lipomatosis: diagnostic and surgical strategy

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The authors report 12 cases of multiple symmetrical lipomatosis (LMS) treated over a 5-year period: diagnosis and therapy are described. Hospitalization in 11 patients was for a functional reason, whereas only one patient required surgery for cosmetic reasons.

Investigations included laboratory blood tests, radiography, ultrasonography and computed tomography to elucidate the extent of the masses. In seven patients, muscle biopsy revealed mitochondrial dysfunction which is still under investigation. There were eight cases of alcohol abuse; seven patients displayed hypertriglyceridaemia and four hyperuricaemia. The lipomas were cervically located in all the patients; in one, a paravertebral extension produced dyspnoea and hindered cervical movement; in another, the oesophagus was displaced by the lipoma.

Surgery included total removal (with or without liposuction), total removal in more than one operation because of the extension of the masses, and partial removal at the patient's request or because of the involvement of important structures.

This study suggests that LMS should be considered as a systemic disease: for this reason diagnosis should be in the light of several types of investigation and various surgical options must be considered.

Primary mucosal melanoma of the oral cavity

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Malignant melanoma arising in the mucosa of the head and neck region is an infrequently encountered clinical entity. The presence of a pigmented lesion in the mucous membranes should raise the suspicion of malignant melanoma. From 1976 to 1991, eight patients presented to this department with primary intraoral mucosal melanoma. Six patients had the lesion on the palate, one on the lower lip and one on the tongue. All patients in this series were men. The mean age of the patients was 48 years. Patients were followed for 6 months to 4 years. The size of the lesion was not recorded in one patient because the primary lesion had been excised elsewhere. However, the remaining lesions were available for clinical assessment. The recorded size varied from 1 to 4 cm and all were melanotic. Recurrence occurred in 63 per cent of patients. Radical surgery was the preferred treatment. Postoperative radiotherapy was applied when doubt existed as to the radicality of the surgical procedure. Survival was found to be independent of sex, tumour site and extent of disease at presentation.

In conclusion, mucosal melanoma of the head and neck continues to result in a poor prognosis in spite of aggressive treatment.

Marjolin ulcers

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Eighteen to 38 per cent of skin cancers may develop from unstable scars, which may originally be chronic ulcers, fistulae, osteomyelitis and longstanding scars. Marjolin ulcer designates the skin cancer originating from chronic burn scars. This predisposing condition is responsible for many skin cancers, mostly squamous cell carcinoma, on unexposed areas of the body, especially on the extremities. Anaplastic change occurs only after many years, and diagnosis is often delayed because of the chronic nature of the original process.

From 1976 to 1991, this department has encountered 41 patients who developed skin cancer originating from a previous burn scar. The duration of the period from the original burn injury to the development of the skin cancer varied from 5 to 55 years. Most of the Marjolin ulcers were on the lower limbs. A biopsy was taken, whenever possible, before surgery of the lesions. Surgical treatment

Plastic and reconstructive surgery

was by radical excision of the lesion followed by grafting or reconstruction by local flaps.

Delay in diagnosis may account for the high incidence of metastatic lymph nodes; the aggressive treatment of the predisposing conditions, currently employed, should therefore reduce the incidence of this variety of skin cancer.

Tissue simulation in teaching surgical technique

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There is an increasing need for junior surgical staff to learn basic surgical techniques before progressing to actual operative experience. A simulated skin preparation has been developed using

siliconized rubber bonded to a latex rubber foam which provides a realistic model of human skin. By altering the relative thickness of the siliconized layer (dermis and epidermis) to the latex layer (subcutaneous), it is possible to reproduce the texture of skin in different parts of the body. With this model the trainee can practise skin suturing, excision of skin lesions, rotation flaps and Z plasty.

Further modifications of the basic skin model have been made to simulate the anterior abdominal wall for laparotomy closure and laparoscopic techniques. In addition, an abdominal and pelvic simulator has recently been completed that can be used to practise a wide range of reconstructive surgery when used along with freeze-dried animal materials. This has been used to simulate low colorectal, coloanal and ileoanal anastomoses, hiatal hernia repair and reconstruction following pancreaticoduodenectomy.

These models provide a valuable method for surgeons in training to develop the skills required in a wide range of surgical procedures before using them on patients.

Rectum and anal canal

St Mark's haemorrhoidectomy: early and late results

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A retrospective study was made of 396 consecutive haemorrhoidectomies performed by one surgeon (U.C.) from 1981 to 1990. The series consisted of 238 male and 158 female patients. Of the operations, 13 per cent were performed as emergency procedures. Patients were followed up until completely healed. All patients received a postal questionnaire 1–5 years after the operation. Complications in the immediate postoperative period included secondary haemorrhage (1 per cent), urinary retention (10 per cent), faecal impaction (1 per cent), severe pain (3 per cent), thrombosis (0.2 per cent) and abscess formation (0.2 per cent). Reoperation in the postoperative period was necessary in 3 per cent of the patients (haemostasis, sphincterotomy, evacuation of faeces). Late postoperative problems consisted of asymptomatic stenosis (2 per cent) and anal fissure (1 per cent). Complications were significantly more prevalent after emergency procedures. Of the patients, 94 per cent considered themselves to be completely healed or much improved after the intervention. Owing to the success of the modern ambulatory treatment of most patients with haemorrhoids, operations tend to be reserved for more extensive pathology and for acute complications. Nevertheless, satisfactory results can be achieved in the great majority of these patients.

Anal advancement flap for the treatment of fistula in ano: an ongoing prospective study

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The common therapy of trans-sphincteric and intersphincteric fistula is usually opening of the fistula track. Healing and continence thereafter are uneventful, but when patients are asked about slight soiling and discharge, many minor complaints become evident.

We have therefore studied a series of patients suffering from intersphincteric, trans-sphincteric, extrasphincteric or supralelevator fistula treated with an advancement flap procedure after excision of the fistula without dissection of any muscle fibre. To date, 23 patients (six women, 17 men) with a mean age of 42 (range 25–75) years have been operated on, including five with Crohn's disease. Thirteen healed primarily and seven failed to heal, with three successful reoperations. Furthermore, two reoperations and three primary operations were done less than 2 months ago and two are needing to be redone (one HIV positive). Fistulae in four of five patients with Crohn's disease operated on during the quiescent phase have healed. The reason for failure was always necrosis of the mucosal flap. No discharge or soiling was reported after a follow-up time ranging from 2 months to 1 year.

In conclusion, advancement flap gives good results with respect to continence. The flap should include not only the mucosa, but also the underlying internal sphincter muscle fibres.

Treatment of deep anal fistula by the flap advancement technique

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The classical treatment of deep anal fistula (the laying-open technique) compromises continence. This study assesses the efficiency of the 'flap advancement' technique in such cases.

From 1977 to 1991, 17 patients (four men and 13 women; mean age 40 (range 24–65) years) underwent this operation. Fifteen had a suprasphincteric fistula, including 12 low rectovaginal fistulae, and two had a deep trans-sphincteric track. Four patients had undergone a previous unsuccessful classical operation. Associated inflammatory bowel disease was noted in eight women with rectovaginal fistula (Crohn's disease in six cases and ulcerative colitis in two cases). The four other fistulae were of obstetric origin. All these patients had a mucomuscular flap advancement. In one case, a diverting colostomy

had been raised previously. In a further case a lateral ileostomy was performed to protect both flap and ileorectal anastomosis (associated subtotal colectomy). No mortality or morbidity was encountered. The median postoperative hospital stay was 9 days. Follow-up was recorded in all patients. Two immediate failures were observed in two cases of Crohn's disease. All the other patients did well, maintaining fistula closure after a median postoperative survey of 64 (range 3–150) months. Functional results were excellent in all but one female patient who complained of minor faecal incontinence.

The flap advancement technique may be considered as an efficient treatment of deep anal fistulae, preserving good anal continence in most cases.

Coping with a perineal stoma

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In order to maintain the body image after a Miles procedure for low rectal cancer, a continent perineal colostomy may be proposed rather than the traditional left iliac colostomy.

The aim of this study was to evaluate the patients' coping with this kind of stoma, taking into account the necessity to perform daily colonic irrigation to achieve faecal continence.

From January 1985 to December 1990, 41 consecutive patients have had a continent perineal colostomy. In January 1991, all patients having a follow-up of at least 12 months were reviewed. From these 18 patients were selected and submitted to a questionnaire by a physician not directly involved in the surgery. All the patients involved replied.

Thirteen patients said that they were at times uneasy with this technique, three seemed unaffected and two anxious.

The main reasons to explain these feelings were: the necessity to perform colonic irrigations (five cases); the fear of having faecal soiling (six cases); and the impossibility of achieving continence of flatus (five cases). Thirteen patients considered that their body image was unaffected, two described a slight modification and three a moderate modification. Two patients were depressed of whom one had had psychiatric troubles in the past.

These results suggest the need to evaluate further the technique of continent perineal colostomy.

Diagnostic value of combined electromyography, proctography and balloon expulsion in the evaluation of anismus in constipated patients

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To investigate the role of electromyography (EMG), proctography (PG) and balloon expulsion test (BET) in the evaluation of anismus and to determine whether this syndrome is characteristic for constipation, 302 patients were studied. A total of 64 constipated patients (male:female ratio 3:61, median age 48 years) underwent combined EMG, PG and BET. EMG was also performed in another group of 148 constipated patients (male:female ratio 26:122, median age 52 years) and compared with 90 incontinent patients (male:female ratio 17:73, median age 59 years). Criteria for anismus during straining were – increase or insufficient (<20 per cent) decrease of EMG activity, decrease or insufficient (<5 per cent) increase of anorectal angle and failure to expel a balloon.

PG, BET and EMG revealed anismus in 3, 58 and 59 per cent respectively of these 64 patients. None of them showed three abnormal tests. In 13 patients (20 per cent) all tests were normal. In 26 patients (41 per cent) two tests were abnormal (most frequently ($n = 24$) EMG/BET) and one normal. In 25 patients (39 per cent) only one test was abnormal. Normal EMG was associated with normal and abnormal BET in 50 per cent of cases. Abnormal EMG was associated with normal and abnormal BET in 37 and 63 per cent respectively ($P = 0.43$, χ^2 test). Comparing slow transit constipation ($n = 12$) and symptomatic rectocele ($n = 26$) the three tests showed

Rectum and anal canal

no significant differences. Anismus, as detected by EMG, was found in 67 of 148 (45 per cent) constipated patients and in 41 of 90 (46 per cent) incontinent patients.

In conclusion, EMG, PG and BET have no diagnostic value in the evaluation of anismus. Anismus is not a characteristic feature of constipation.

Diffuse cavernous rectal haemangioma: clinical appearance and sphincter-saving approach to therapy

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Diffuse cavernous haemangioma of the rectum and rectosigmoid colon is an extremely rare condition. One case of diffuse cavernous haemangioma and one of diffuse mixed capillary and cavernous haemangioma of the rectum and rectosigmoid colon are reported. The presentation and management are compared with those of 37 cases reported in the literature.

The two cases presented were treated using a pull-through procedure with a stapling gun 2 cm from the dentate line. One of the patients also had bladder haemangioma treated with laser photocoagulation. Both patients remained continent and had minor episodes of rectal bleeding not requiring iron or transfusion therapy after operation.

The mean age of the 39 patients was 27.2 (range 6–57) years. Mean age at onset of rectal bleeding was 7.2 years, sex ratio (M:F) 1.85:1 and massive bleeding episode rate was 36 per cent. Mucocutaneous lesions were seen in 20 per cent, and phleboliths in 54 per cent. Barium enemas were usually not diagnostic. The diagnostic rates of proctoscopy and biopsy were 87 and 29 per cent, respectively. Massive bleeding after rectosigmoid biopsy occurred in 25 per cent. Arteriography was diagnostic in 47 per cent. Fifty-one per cent of the patients had had at least one operation in the past, haemorrhoidectomy being the most common. The ratio of cavernous to mixed cavernous and capillary haemangiomas was 12:1. The surgical treatment was abdominoperineal resection (APR) in nine and sphincter-saving procedures (SSP) in 24 patients. Recurrent bleeding occurred in 21 per cent of the patients treated with SSP. The complication rate was the same with both APR and SSP (33 per cent).

In conclusion, this rare lesion should be suspected in patients with rectal bleeding, and diagnostic investigations should be performed before any surgical treatment. As the complication rates are identical in the groups treated with APR and SSP, SSP should be the treatment of choice for treatment of diffuse cavernous haemangioma of the rectum whenever possible.

Rectal prolapse in adults: treatment by anterior resection of the rectum

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Since 1990 we have conducted a prospective study of anterior resection of the rectum for rectal prolapse in adults. The patients consisted of three men and eight women who complained of chronic constipation, perineal pain and the impression of the presence of a perineal mass upon defaecation. Only one patient complained of faecal incontinence.

Preoperative investigation included barium enema, rectoscopy, excretion proctography, anal manometry, cystography, perineal electromyography and peritoneography. This demonstrated nine cases of anterior external anorectal prolapse and two of procidentia interna.

Eleven patients had a redundant sigmoid, seven had an associated cystocele and one patient had a solitary ulcer of the rectum. All the patients underwent anterior resection of the rectum including the sigmoid loop with a stapled end-to-end anastomosis using the 'triple stapling' technique, the last case by a laparoscopic approach. The cystoceles were treated at the same time by the Marshall–Marchetti technique.

There was no mortality. Ten patients reported less constipation, and nine patients reported the disappearance of perineal discomfort. One patient showed no improvement. Excretion proctography at the

third month after operation showed correction of the preoperative anomalies in ten patients. Manometric values were unchanged after surgery in the 11 patients studied.

Rectopexy with or without sigmoid resection

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Constipation and painful defaecation are the most frequent symptoms associated with rectal prolapse. For a large percentage of patients, rectopexy alone does not improve symptoms (with the exception of incontinence) but, on the contrary, it aggravates them. For this reason, some surgeons prefer to combine rectopexy with sigmoid resection.

In our department, between 1985 and 1990, 35 patients (29 women and six men) underwent surgery for rectal prolapse. Mean age for women was 65 years and for men 38 years. The diagnosis was total rectal prolapse in 19 patients, rectocele and internal rectal procidentia in 14 patients, and solitary rectal ulcer in two patients.

Twenty-six operations were performed via the abdominal approach, and in nine the perineal or transanal approach was used. Operative techniques were: 20 Ripstein, six Orr–Loygue, four Delorme, three Sullivan and two resections. Twenty-eight patients (80 per cent) were contacted or seen for follow-up. By analysing our results and a literature review, we attempt to define which patients will not improve following rectopexy alone, and in which rectopexy should be combined with sigmoid resection.

Carcinoma of the anal canal: utility of the tumour marker squamous cell carcinoma antigen in diagnosis and follow-up after surgery and/or radiotherapy

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Squamous cell carcinoma (SCC) antigen may be a useful tumour marker in SCC of the cervix, lungs, head, neck, oral cavity and oesophagus. The aim of this study was to find out the sensitivity and prognostic significance of SCC antigen in 31 patients with carcinoma of the anal canal.

Patients were treated by surgery and radiotherapy. The initial expression and post-therapeutic serum levels of SCC antigen were measured.

Of the patients 20 per cent showed pretherapeutic SCC antigen levels above 2.5 ng ml^{-1} (cut-off level). Levels of SCC antigen measured during therapy reflected in all cases success or failure of therapy. Strongly positive SCC antigen serum levels indicated poor prognosis. After therapy, a positive result for SCC antigen indicated the presence of residual tumour.

Results show that SCC antigen, although being of low sensitivity, could represent a useful tumour marker in monitoring response to therapy and in predicting relapse of the tumour.

Faecal stasis and pouchitis: an experimental study

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This experimental study was conducted in 19 beagle dogs to investigate the role of bacteria and their metabolites in the pathogenesis of pouchitis. After subtotal colectomy an ileostomy was constructed with (nine) and without (ten) prestomal reservoir. Ileal effluent, bacterial flora and mucosal morphology were analysed before and after a 6-week period of progressive, intermittent stoma occlusion in five dogs with conventional ileostomy (group II) and in five dogs with reservoir (group III). The same analysis was performed in four dogs, before and 12 weeks after the construction of a continent ileostomy (Kock pouch, group IV). Group I (five, no reservoir, no occlusion) served as the control group. Ileostomy occlusion in group II did not alter anaerobic flora compared with

group I (numbers: 0.06×10^9 and 0.02×10^9), whereas in groups III and IV increased amounts of anaerobes were found (42×10^9 and 190×10^9).

After the occlusion period, mucosal morphology in group II did not differ from that in group I. In contrast, all reservoirs showed chronic inflammation with slight mucosal atrophy. In group II, ileostomy occlusion did not alter blood group antigenicity of intestinal glycoproteins, whereas in groups III and IV this antigenicity completely disappeared, indicating breakdown of the protecting glycoprotein layer. This phenomenon was associated with

a significant increase of glycolytic activity in groups III and IV. Compared with group I, proteolytic activity was reduced in groups II, III and IV. The longer the duration of occlusion, the more this activity was reduced. However, in group IV proteolytic activity did not disappear, despite almost continuous occlusion.

We conclude that chronic inflammation of ileal reservoirs is caused by overgrowth of anaerobes. These organisms produce an increased amount of glycolytic enzymes, resulting in breakdown of protecting mucosal glycoproteins. Further damage might occur as a result of persistent proteolytic activity.

Splenectomy for splenomegaly exceeding 1000 g: analysis of 47 cases

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Patients who underwent splenectomy for splenomegaly exceeding 1000 g ($20 \geq 1000$ g, $27 \geq 1500$ g) were studied retrospectively to establish the risks and benefits of this operation.

Between May 1981 and May 1991, 29 men and 18 women with a mean (range) age of 56.2 (19–87) years were included in a total of 152 patients referred to our department for splenectomy for haematological indications. Malignancy was the most common disorder ($n = 42$).

The main indications for splenectomy were cytopenia ($n = 20$), diagnosis ($n = 14$), initial treatment ($n = 8$), pain ($n = 4$) and spontaneous rupture ($n = 1$). Midline laparotomy was used in all cases, with preoperative arterial embolization in 25. Ten patients underwent an associated surgical procedure. One patient died (2 per cent) and 12 (26 per cent) had postoperative complications with a favourable outcome except for one patient who needed reoperation.

The advantages of splenectomy include histopathological diagnosis in 13 of 14 cases of splenomegaly of unknown origin, effective initial treatment in polymphocytic and hairy cell leukaemias, definitive relief of pain in all cases and long-term improvement of cytopenia in most cases.

In conclusion, the mortality rate of splenectomy for massive splenomegaly is not very different from that of splenectomy for haematological disorders with normal spleen weights. The prognosis of haematological malignancies is not modified by splenectomy. Splenectomy, however, plays an important role in palliative management, improving the quality of life of these patients.

Splenic abscess: early diagnosis and treatment options

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Splenic abscess remains an unfamiliar and poorly studied entity. The availability of ultrasonography and computed tomography (CT) has significantly improved diagnostic efficiency.

This study presents six cases of splenic (two solitary and four multiple) abscesses treated in this hospital from 1982 to 1990. The signs and symptoms were non-specific, temperature elevation and abdominal pain always being present. The diagnosis was based on abdominal CT (five cases) and ultrasonography (one case).

The early treatment was appropriate antibiotics. When splenic abscess was demonstrated, emergency splenectomy was performed in two patients and delayed splenectomy in two others, after onset of a new pyrexia and recurrent septic signs. In two cases abscess resolution was observed by repeated CT evaluation. Percutaneous drainage was not used. None of these six patients died and the follow-up (1–9 years) confirmed complete recovery.

In patients with persistent fever and intra-abdominal infection a combination of broad-spectrum antibiotics and splenectomy remains the recommended treatment. If clinical recovery occurs rapidly after administration of antibiotics, we suggest delay of splenectomy under meticulous clinical and radiological surveillance. Early detection of occult and uncomplicated splenic abscesses by improved radiological imaging techniques may identify a group of patients who can be successfully managed by antibiotics alone.

Splenectomy in patients with haematological diseases

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We have reviewed 235 patients with various haematological diseases who have undergone splenectomy at our department during the period between 1970 and 1990. There were 133 men (56.6 per cent) and 102 women (43.4 per cent). The mean age of the patients was

49.6 (range 16–81) years. The most common diagnosis was haemolytic anaemia, followed by thrombocytopenic purpura, spherocytosis, Hodgkin's disease, hairy cell leukaemia, chronic lymphatic leukaemia, non-Hodgkin's lymphoma and myelofibrosis. In all patients the splenic bed was drained. During the immediate postoperative period the mortality rate was 1.2 per cent (two patients died from overwhelming postsplenectomy sepsis) and morbidity was 3.5 per cent. During the late postoperative period, however, both mortality and morbidity were increased, depending on the haematological disease and the asplenic state of the patients, despite prophylaxis with penicillin and pneumococcal vaccination. It is concluded that elective splenectomy in haematological disease is a safe procedure even in high-risk patients, but it is recommended that close cooperation between the surgeon and haematologist during the perioperative period is essential, and that close medical surveillance is undertaken thereafter.

Heterotopic autotransplant of the traumatized spleen

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Splenectomy performed for ruptured traumatic spleen causes early and late complications resulting from the absence of splenic function. One of the possibilities for preserving splenic function is a splenic autotransplant (SAT). The major indication for SAT is haemostatic splenectomy for children and young people. SAT was performed on nine patients with traumatic splenic rupture by implanting splenic fragments ($50 \times 10 \times 5$ mm) in 'pockets' created in the free side of the great omentum. Follow-up on the second, seventh, tenth and 21st days after surgery showed the return of normal splenic function on the 15–17th days after the operation. Thrombocytic crisis was absent or reduced, Howell-Jolly bodies did not appear and the serum immunoglobulin M level was normal. Ultrasonographic images of the grafted splenic parenchyma were normal, without signs of perigraft collection. The only ultrasonographic change was a slight gradual decrease in the volume of the grafts seen in the first 3 months after surgery. Scintigraphy with ^{99m}Tc -labelled erythrocytes damaged by heat, performed between 2 and 45 months after SAT, confirmed the heterotopic site of tracer uptake.

In our opinion, SAT allows the maintenance of splenic function. It is simple and inexpensive. Furthermore, it does not prolong the operation significantly, there are practically no surgical risks and benefit is likely.

Haemoperitoneum due to splenic laceration: conservative laparoscopic treatment

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A patient with a ruptured spleen was recently treated by laparoscopy. The patient, a 31-year-old male car accident victim, came under our care with abdominal trauma and a fractured right olecranon. Abdominal computed tomography (CT) showed rupture of the spleen and a collection in the left hypochondria. Laparoscopy was performed under general anaesthesia; after introduction of the periumbilical laparoscope two other ports with 10 cm between them were introduced. A volume of 400 ml of bloody liquid was aspirated and the front of the spleen appeared to be covered by clot. After washing, a transverse rupture extending to the hilum was seen. There was little bleeding, only a slight trickle of blood leaking from the wound. A few millilitres of fibrin glue was then applied and the wound was covered with omentum. Under direct vision, three tubes were positioned, one in the right hypochondria, one in the left, and a third near the splenic hilum. Continuous peritoneal lavage was started through the latter. During the following days the washing was clear and haemodynamic conditions of the patient were stable. The tubes were then removed, two on the third day and the last on the fourth. A further CT scan was performed, which after 10 days showed disappearance of the rupture of the spleen.

In this case, the patient benefited from splenic conservation without laparotomy.

Splenectomy alters early host response to intra-abdominal sepsis

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Septic sequelae of splenectomy are well recognized, but the mechanisms are unclear. Macrophage activation may be detrimental during the acute septic response. The effects of splenectomy on peritoneal macrophage activation (superoxide anion (O_2^-)) were evaluated. Study 1 (*in vitro*): female CD-1 mice were randomized to receive no treatment (control), laparotomy, or laparotomy and splenectomy; 24 h later, peritoneal cells were harvested and studied for cell kinetics and macrophage O_2^- production. Study 2 (*in vivo*): mice were randomized to laparotomy or laparotomy and splenectomy, subjected to simultaneous caecal ligation and puncture and studied for mortality.

	Study 1 (n = 40)			Study 2 (n = 50)
	Total cells (percentage)	Macrophage (percentage)	O_2^- generation (nmol 90 min ⁻¹)	survival (percentage 24 h ⁻¹)
C	5.3(0.3)	47(2)	0.5(0)	—
L	8.7(0.7)	42(2)	1.7(0.2)	56
L+S	18.0(3)*	25(3)‡	2.5(0.7)*	32†

Values are mean(s.e.m.). C, control; L, laparotomy; L+S, laparotomy and splenectomy. * $P < 0.05$; † $P < 0.02$; ‡ $P = 0.001$ versus other groups

Laparotomy was associated with an influx of inflammatory cells into the peritoneal cavity but percentage macrophage content was unaltered. Laparotomy and splenectomy was associated with a significant increase in inflammatory cells in the peritoneal cavity but percentage macrophage content was significantly reduced. Superoxide release was increased after injury, but significantly so only in the laparotomy and splenectomy group. Highest levels of macrophage activation (laparotomy and splenectomy) correlated with the significantly higher mortality seen in this group.

These findings demonstrate a novel role for the spleen in regulating peritoneal cell fluxes and function during the acute inflammatory response, and indicate a mechanism through which splenectomy may predispose to mortality from early sepsis.

Role of the spleen in antibody formation to encapsulated bacteria

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The role of the spleen in antibody formation against encapsulated bacteria is illustrated by the increased frequency of pneumococcal infections (sepsis) in splenectomized patients as well as the poor antibody response to capsular polysaccharide (PS) antigens in these patients.

Capsular PS of *Streptococcus pneumoniae* are so-called T cell-independent type 2 antigens. The major characteristics of the immune response to this class of antigens are late onset of responsiveness in ontogeny and lack of immunological memory. The spleen is a major site of PS antigen handling and presentation; upon immunization, PS antigens localize selectively to the splenic marginal zone macrophages. Onset of anti-PS responsiveness *in vivo* (2 years of age in humans) coincides with appearance of B lymphocytes in the marginal zone of the spleen that express complement receptor 2 (CR2; CD21). Co-ligation of the antigen receptor and CR2 synergizes in B lymphocyte activation, especially in B lymphocyte activation by polysaccharides. Indeed, upon activation *in vitro* with PS, splenic B lymphocytes can generate high numbers of anti-PS antibody-secreting cells.

It should be noted that most studies dealing with anti-PS antibody responses following splenectomy concern patients with potential underlying or induced immunodeficiency (Hodgkin's disease, idiopathic thrombocytopenic purpura). The anti-PS antibody response of congenital asplenic patients in general is normal. The increased risk for pneumococcal infections postsplenectomy therefore is not entirely based on an insufficient antibody response: the spleen probably also has a major role in removal of opsonized

bacteria. Both vaccination with pneumococcal polysaccharides and antibiotic prophylaxis are therefore indicated in prevention of postsplenectomy pneumococcal sepsis.

Spleen-saving techniques and partial splenectomy

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The overwhelming postsplenectomy infection syndrome appears to be fatal in approximately half of the cases when it occurs in children and in one-third of the cases when it occurs in adults. After splenic injury the aim is to save functional splenic tissue rather than total splenectomy. Known methods of preserving splenic tissue are non-surgical treatment, surgical repair, or autotransplantation. With the use of a preservation technique it is essential to preserve 25 per cent or more (quantitatively) of the splenic tissue, vascularized by the original splenic artery and vein. Only then will a good filtration function of the blood be guaranteed.

A new technique of applying collagen fleece on lacerations and cut surfaces together with total wrapping of the mobilized, ruptured spleen with mesh is presented. The mesh gives a packing and surface compression of the splenic fragments and prevents dislocation of the haemostatic fleece. This 'shower-cap' technique can be applied to ruptures independently of course and extent. Moreover, no special instruments are needed.

In addition, the 'decapsulation' technique is presented, a useful alternative for the resection of benign splenic cysts independently of their localization, and which preserves the essential hilar splenic vessels. With the above preservation techniques protection against overwhelming postsplenectomy infection syndrome is guaranteed. No vaccination and no antibiotic prophylaxis are needed.

Autotransplantation of the spleen

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After splenectomy there is a high risk of sepsis, the so-called overwhelming postsplenectomy infection syndrome (OPSI), with a high mortality rate especially in children. This syndrome may be caused by a defect in the immune system after splenectomy. Animal experiments suggest that autotransplantation of splenic tissue (ATS) after splenectomy could restore these defects.

The problem with ATS in humans is the evaluation of functional activity and differences in immune capacity after splenectomy with and without ATS. Most of the investigations have used ^{99m}Tc-colloid scintigraphy, peripheral blood smears and immunoglobulin levels.

Recently we studied immunological function in 24 patients after splenectomy for traumatic rupture, or rupture during partial gastrectomy because of peptic ulcer. In ten patients ATS was performed with 20–30 g splenic tissue in the greater omentum. From the non-ATS group eight patients were demonstrated to have splenosis and six were without splenic activity.

The following tests were performed: Fc-receptor test by IgG-coated and ^{99m}Tc-labelled red cells after incubation with antirhesus (D) antiserum (scintigraphy and blood clearance); primary immunological response after immunization with *Helix pomatia* α-haemocyanin and after immunization with polyvalent pneumococcal vaccine (Pneumovax-23; Morson, Hoddesdon, UK); granulocyte function by nitroblue tetrazolium test, phagocytosis-killing test and a phagocytosis and opsonizing capacity test; lymphocytic B/T ratio; several complement factors (Clq + C3c + C3d + C4); transferrin, and immunoglobulins.

Until now the outcome of tests on the specific mononuclear phagocytic immune system have not shown many differences between the three patient groups and between patient groups and standard levels. However, specific immunological studies are now in progress to evaluate the effect of ATS on the humoral response capability with respect to different *Pneumococcus* subtypes and to determine complement activity.

Trauma of the spleen in children

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In the last two decades, the management of splenic injuries in children has changed significantly since it has become clear that the

Spleen

asplenic state carries the hazard of overwhelming postsplenic infection (OPSI). OPSI has a high mortality rate (50–80 per cent) and occurs more frequently in the younger age group. The spleen as a biological filter, its important role in immune defence and its capability of healing are the reasons for either non-operative or operative attempts at splenic preservation.

The diagnosis of splenic injury after blunt abdominal trauma may be difficult. Ultrasonography, computed tomography and diagnostic peritoneal lavage are applied in traumatized children as they are in adults. Non-operative treatment is pursued in clinically haemodynamically stable patients.

This management is successful in approximately 90 per cent of paediatric patients, which is in contrast to the 15–20 per cent success rate in adults. Part of this difference is due to the composition of the splenic capsule, which provides better haemostatic properties in children.

Indications for operative treatment are persistent tachycardia/hypotension despite adequate fluid resuscitation, and a blood transfusion requirement exceeding 20 ml kg^{-1} for the first 3–6 h. The degree of splenic injury dictates the operative method; there is no difference in the rebleeding rate after splenorrhaphy or after splenectomy (1 per cent). Unless the patient is in a condition that prevents prolonged surgery or if the damage is beyond repair, salvaging the spleen should always be the goal.

Splenic infarction: a post-mortem study of 75 cases

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Many cases of splenic infarction are reported in the literature, but the clinical implications of this pathology with regard to causal factors and associated diseases are rarely described. In an autopsy study the primary and associated disorders are reviewed.

In a series of 2713 deaths, 75 splenic infarctions were identified. The incidence of the pathology in the population studied was 2.7 per cent and the mean age at death was 61 years. An increased spleen weight was frequent (average spleen weight 350 g). Systemic embolism was demonstrated in 30 patients. In 17 subjects there were three or more concomitant infarctions in other organs. A total of 38 patients had a severe aortic pathology. In patients with embolism after angiography or cardiovascular surgery, dislodged cholesterol crystals could be demonstrated in different organs. Endocarditis was

present in 12 subjects, and in cases of infective endocarditis metastatic abscesses were common. Haematological pathology was the source of infarction in 13 patients. Other aetiological factors included pneumonia, acute respiratory distress syndrome, pancreatitis and non-haematological malignancy. They were due to circulatory failure or compression of the splenic vessels. Anatomical anomalies were rare.

We conclude that splenic infarction occurred: (1) by embolism in cardiovascular, haematological, and infectious diseases; (2) by vein thrombosis in splenic congestion; and (3) by general or local circulatory failure in pulmonary, neoplastic and pancreatic diseases. All cases of splenic infarction were secondary to a primary disorder. If the disease seems to be the only feature supplementary investigations are necessary to detect a possible silent pathology.

Experimental and clinical follow-up of autotransplanted splenic graft

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The integrity of the autotransplanted splenic graft (ASG) was documented both experimentally and clinically by implanting fragments of splenic tissue in the great omentum. The experiment was performed on three groups of 30 Wistar rats each, with splenectomy followed by splenic autotransplantation (SAT). Biopsies were performed 7, 14 and 21 days after SAT. A progressive appearance of newly formed capillary vessels was noticed at the omentum-ASG interface in most of the experimental animals. On day 7, the sinusoids of the red pulp appeared to have collapsed. On day 14 granulation tissue formed a pseudocapsule around the ASG. On day 21, the peripheral sinusoids of the red pulp were open. The ASG was repopulated by lymphocytes, possibly through their affinity to splenic surface antigens. Histological and functional recovery of the splenic tissue was demonstrated.

The clinical study included nine patients followed up for 21 days, who showed a good clinical course, a short or absent thrombocytic crisis, and normal immunoglobulin M levels. No significant ultrasonographic changes of graft splenic parenchyma were seen. Scintigraphy with $^{99\text{m}}\text{Tc}$ -labelled erythrocytes at intervals from 2 to 45 months after surgery confirmed the ASG integrity through active heterotopic uptake. The SAT method may have a role in the surgical treatment of the traumatized spleen.

Thoracic surgery

Therapy for primary and secondary tumours of the thoracic wall

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In the treatment of extensive malignant chest wall tumours, surgical procedures are currently integrated in a multidisciplinary approach to therapy. From 1985 to 1990, we treated six patients suffering from a malignancy that originated from structures of the thoracic wall. There were two young female patients, 16 and 27 years old, with a poorly differentiated neuroectodermal tumour, and two 17-year-old male patients with Ewing's sarcoma and a mesenchymal chondrosarcoma. In these patients, preoperative chemotherapy (CESS and CWS protocols) produced shrinkage of the tumour which was then resected. After operation, the tumour site was irradiated and chemotherapy continued. Two of these patients died from metastatic disease 2 and 5 months after the operation. A further two male patients, 47 and 66 years old, had surgery for a dermatofibrosarcoma.

More common than these primary tumours of the thoracic wall are secondary malignancies, arising from breast cancer or bronchogenic carcinoma and thus protruding into the chest wall. Under these circumstances, surgery is still considered the most promising approach with simultaneous excision of both the chest wall and the primary tumour. Chemotherapy or irradiation merely has an adjuvant role. In the 6-year period, we operated on 13 patients (11 men) with an average age of 60 years. In spite of potentially radical surgery, life expectancy in these patients is rather short. In ten patients the tumour was poorly differentiated or undifferentiated. Six of these patients died within 10 months of surgery from continued tumour growth.

Latissimus dorsi muscle flap after thoracotomy for tumours invading ribs

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The experience is reported of 14 cases of chest wall reconstruction with latissimus dorsi flap (11 for lung cancer and three for breast cancer, both invading the ribs) among 36 thoracotomies performed in the same period. Primary and metastatic tumours are not included in this series.

Chest wall defects were anterior, anterolateral and lateral in five, six and three cases, respectively, and involved two, three or four ribs in five, seven and two cases, respectively. The procedure was radical in 12 cases. Eleven *en bloc* resections with lung and three with soft tissue were performed. Reconstruction was achieved by a latissimus dorsi flap transposition in thoracotomies performed for lung cancer, and a musculocutaneous flap in those performed for breast cancer. There were no deaths at 30 days and no serious complications were observed except for a partial cutaneous necrosis and wound infection in three cases. In all cases good stabilization of the chest wall was achieved.

Two patients in whom the procedure was performed to relieve symptoms died within 6 months of surgery. One patient survived 18 months, four died within 24 months, five died after 2 years and only two are alive at 3 years. Latissimus dorsi was effective in the reconstruction of wide chest wall defects both as single and musculocutaneous flaps while survival depends upon the basic pathology.

Indication for lung resection in pneumonia or lung abscess

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Pneumonia and lung abscess usually respond to adequate antibiotic treatment and physiotherapy. When these conditions persist they may be treated by resection of the responsible lung segment. This is especially important in critically injured patients in which aspiration,

rib fractures, atelectasis or lung contusion lead to untreatable complications.

In the past 10 years we have operated on ten critically injured patients and another seven patients, all suffering from severe, persisting pneumonia. Resection involved the right upper lobe (two patients), the right lower lobe (seven), the left lower lobe (six), the right middle lobe (one) and the left upper lobe (one). Histological examination showed an abscess in ten patients, and a chronic pneumonia in seven patients. Seven patients died after operation.

Because of the high mortality rate, we believe that a lung resection should be performed early in patients suffering from a persisting pneumonia or a lung abscess localized to one part of the lung and with septic complications. Resection should be considered, especially in patients with multiple trauma.

Second primary lung cancer after bronchial sleeve resection: treatment and results in 11 patients

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During the years 1960–1989, 145 patients underwent sleeve lobectomy or sleeve resection of a main bronchus. Follow-up was complete except for one patient who was lost to follow-up 4 years after operation. Eleven patients (7.6 per cent) developed a second primary cancer in the lung, of whom ten were men. Mean (s.d.) age at sleeve operation was 61.2 (11.6) years. Mean interval between sleeve operation and development of the second primary was 53.8 (range 6–197) months. All second primaries occurred on the contralateral side. Different histology from the primary tumour was present in five patients.

Seven patients (64 per cent) were operated on: five underwent lobectomy and two segmentectomy. In one further patient the tumour was judged to be irresectable. Chemotherapy was given to two patients with small cell carcinoma and radiotherapy to one patient who presented with bone metastases.

Follow-up was complete for the 11 patients. Data were calculated from the moment of detection of the second primary. There was one postoperative death due to myocardial infarction. Five other patients died during follow-up. The 1- and 4-year actuarial survival rates were 46 per cent and 31 per cent. For the operated patients, 1- and 4-year survival rates were 69 per cent and 46 per cent.

Sleeve resection is a valuable method for preserving functional lung tissue, offering a chance of subsequent resection with acceptable results in patients who develop a second primary cancer.

Bronchiectasis: current indications and timing for surgery

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Despite continuous improvement in the medical treatment of bronchiectasis, a number of patients will eventually require surgery. The optimal timing of surgical resection and the efficacy of surgery need to be reassessed in this context.

The records of 77 patients undergoing operation for bronchiectasis during 1972–1991 were reviewed. There were 38 men and 39 women aged 17–72 (mean 39) years. Four patients underwent repeated surgical resections. Long-term results could be assessed in 66 patients (86 per cent) either by questionnaire or by subsequent medical evaluation.

Indications for surgery were persistent symptoms under medical treatment in 38 cases (49 per cent), local complications such as fungal superinfection or severe bleeding in 19 (25 per cent) and 12 (16 per cent) respectively, and pulmonary mass lesions in eight (10 per cent). Limited resections such as segmentectomies or lobectomies were carried out in 73 cases (95 per cent). In patients with localized disease ($n = 40$), surgery led to significant improvement in 36. In patients with extensive or complicated disease ($n = 30$), surgery was often more aggressive (four pneumonectomies), and four postoperative deaths occurred in debilitated patients. In the remaining 26 patients, long-term results of surgery were satisfactory in 17 and poor in nine.

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Patients with localized disease and recurrent symptoms despite medical treatment should undergo operation before the occurrence of complications. At this stage, surgical resection can be limited and has the potential to cure or significantly improve the patient's condition. In contrast, patients with extensive disease are often debilitated and surgical treatment is less rewarding and sometimes poorly tolerated.

Results of 8 years of trans-sternal thymectomy for myasthenia gravis

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Thymectomy has gained increasing popularity in the past few years as the most effective treatment of myasthenia gravis. This study reviews our 8 years' experience of using thymectomy for myasthenia gravis.

From 1983 to 1991 we operated on 32 patients with myasthenia gravis: 18 (56 per cent) women and 14 (44 per cent) men, aged 19–78 (mean 47.5) years. At surgery, 16 (50 per cent) were at Osserman's stage IIA, 14 (44 per cent) at stage IIB and two (6 per cent) at stage III. The diagnostic procedures included: chest radiography in all cases; computed tomography of the chest in all cases (eight of nine thymomas discovered before operation); tensilon test in all cases (all were positive); electromyography in 23 cases (19 were altered); and acetylcholine receptor antibody was detected in 15 of the 25 tested. We performed a trans-sternal total thymectomy in all cases (including all continuous mediastinal fat and any suspicious tissue that might contain islands of ectopic thymus). The follow-up ranged from 3 months to 8 years (mean 3 years 2 months).

There was one postoperative death from respiratory insufficiency and sepsis (82-year-old patient at Osserman stage III, who died during preoperative plasmapheresis). Postoperative morbidity occurred in seven (22 per cent) patients: pneumonia (two cases), wound infection (one case), slow wound healing (two cases) and pleural effusion (three cases). Improvement was achieved during the first 6-month period in 22 of 30 (73 per cent) patients and permanent improvement (more than 3 years) in 13 of 24 (54 per cent) patients. Of the remaining patients, five now follow a lower drug dosage treatment, and four follow the same or a higher drug dosage treatment than before thymectomy. We found 19 cases of thymic hyperplasia (59 per cent), nine thymomas (28 per cent) and normal thymic involution in four cases (12 per cent).

Given these results, we conclude that thymectomy is the treatment of choice for generalized myasthenia gravis. It offers a satisfactory percentage of clinical improvement with low morbidity and mortality rates, and it also provides treatment of unexpected thymomas.

Surgery for lung tuberculosis and related lesions: change in clinical presentation as a consequence of population migration

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In spite of better healthcare organization and continuous improvement in medical treatment, the number of patients treated for lung tuberculosis is steadily increasing in our region. Consequently the number of patients referred for surgical treatment remains high.

A total of 92 consecutive patients needing surgery for lung tuberculosis and related lesions in our institution from 1972 to 1991 was studied to determine the type of patients requiring surgery and the mode of presentation of the illness.

Indications for surgery were as follows: failure of medical treatment in 12 (13 per cent) cases, mass lesions of the lung and mediastinum in 28 (30 per cent) and 11 (12 per cent) cases respectively, advanced forms of disease such as complications of previous operations in six (7 per cent) cases or secondary complications (empyema, haemoptysis, bronchiectasis, aspergilloma) in 35 cases (38 per cent). Forty-three patients (47 per cent) were of foreign origin and had migrated recently to our country; 26 of these (60 per cent) presented with advanced forms of tuberculosis and 11 (26 per cent) were debilitated by other diseases, compared with 24 (49 per cent) and 11 (22 per cent) respectively of the 49 local patients. Concomitant factors favouring advanced forms of disease were predominantly chronic alcoholism in the local group and immune

defects or diabetes in the foreign group. The operative mortality rate was 2–4 per cent in both groups.

In contrast to other reports, the number of patients operated on for lung tuberculosis has not declined in our region. Migration of population accounts for this difference as nearly half of the patients who needed surgery were of foreign origin. They also presented with more advanced forms of disease, often complicated by lung destruction and aspergilloma. This change of presentation of lung tuberculosis is a new challenge to our local strategy to prevent and treat this disease.

Adenine nucleotide degradation in ischaemic rabbit lung tissue

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The endogenously generated nucleosides (adenosine and inosine) and bases (hypoxanthine and xanthine) are important in lung reperfusion injury. The present study investigated the catabolism of adenosine 5'-triphosphate (ATP) during lung ischaemia. ATP and its catabolites were measured in deflated rabbit lung tissue immersed in 0.9 per cent saline solution at 37°C. Measurements were made at 0, 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180, 210 and 240 min.

The preischaemic value of ATP in lungs was 9 $\mu\text{mol/g}$ dry weight⁻¹ ($n = 6$). At 10 min warm ischaemia, rapid breakdown of ATP and an increase in adenosine 5'-monophosphate (AMP) were demonstrated. Hypoxanthine was identified as the major catabolite.

During lung ischaemia, there is an increase in both adenosine and inosine 5'-monophosphate (IMP). On adding erythro-9-(2-hydroxy-3-nonyl)adenine (an adenosine deaminase inhibitor) to the flushing solution, adenosine becomes the major catabolite, with levels of 4 $\mu\text{mol/g}$ dry weight⁻¹, indicating that the breakdown of AMP to adenosine in ischaemic lung tissue is more important than the breakdown of AMP to IMP. The endothelial cell has the potential to degrade adenosine to hypoxanthine. Nucleoside transport inhibitor inhibits the uptake of adenosine in the endothelial cell. During lung ischaemia, it had no effect on the formation of nucleosides and bases. ATP seems to be catabolized to hypoxanthine without transport of adenosine over cellular membranes. Because hypoxanthine is accumulated in endothelial cells, this suggests that ATP metabolism of lung tissue is mainly located in endothelial cells. We conclude that the ATP level in the preischaemic lung is 9 $\mu\text{mol/g}$ dry weight⁻¹. ATP is catabolized to AMP, which is mainly dephosphorylated to adenosine rather than deaminated to IMP. During lung ischaemia, hypoxanthine is the major catabolite.

Apical parietal pleurectomy with resection of bullae by videothoracoscopy: new outlook for surgical treatment of spontaneous pneumothorax

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To minimize the risks of thoracotomy we have performed pleurectomy as a treatment of spontaneous pneumothorax using videothoracoscopy. The operation was performed under general endobronchial anaesthesia, with the patient placed in the posterolateral thoracotomy position. Three trocars inserted through the fifth, seventh and ninth intercostal spaces allowed the introduction of thoracoscopic instruments. The apical pleurectomy was delimited by the sixth rib, internal thoracic vessels, costovertebral sulcus and the first rib. Blebs and small bullae were transected with an EndoGIA 30 (US Surgical) stapler. The pleural cavity was drained through the lower orifices.

This procedure was performed in 18 patients presenting with 20 spontaneous pneumothoraces. Operative indications were: persistent air leak (seven cases), recurrence (nine cases), bullae with adhesions and/or anterior thoracotomy for spontaneous pneumothorax (four cases). The only complication was one case of bleeding of 200 ml from a wounded intercostal vessel (ligated with a clip). Operative duration decreased from 2 h to 1 h. Average duration of drainage was 3.5 days and hospital stay 4.5 days. There was no death nor were there any immediate complications. Postoperative pain was found to be less than after pleurectomy with thoracotomy in all cases.

This original procedure is the first described to be performed entirely through thoracoscopy with non-specific instruments and has significant economic implications. Open pleurectomy will probably remain the most efficient pleurodesis procedure. However, with thoracoscopy, pleurectomy will certainly be freed from its main disadvantages of thoracotomy-related pain and haemorrhagic complications. This might make it possible to extend pleurectomy to patients with respiratory insufficiency and also to young patients. This hypothesis must be assessed by prospective controlled trials.

Tumour cells in intraoperative pleural lavage as a prognostic factor in lung cancer

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In a prospective study, pleural lavage with 300 ml physiological saline was performed at thoracotomy before (lavage I) and after (lavage II) resection of lung cancer. In all, 178 patients (132 with lung cancer and 46 with non-neoplastic lung disease) underwent pleural lavage. The lavage fluid was centrifuged and the sediment embedded in paraffin for cytological examination.

Tumour cells were found in 56 patients at lavage I and in 48 at lavage II. Among those previously classified as stage I ($pT_{1-2}N_0$), tumour cells were demonstrated in 24 patients (30 per cent). All controls were negative. The cumulative 4-year survival rate of curative resected stage I non-small-cell lung cancer was 23 per cent if lavage was positive and 63 per cent if negative ($P < 0.05$).

The detection of tumour cells in intraoperative pleural lavage corresponds to a pT_4 stage of lung cancer with a poor life expectancy. Cytological examination of an intraoperative pleural lavage should be carried out when assessing tumour stage.

Selection criteria for lung metastasectomy

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Metastatic disease can be treated by surgery, especially metastases in the first systemic filter. A total of 83 patients had lung metastasectomy (period 1977–1991): 17 osteosarcomas, 21 soft tissue sarcomas, 11 melanomas, 12 colorectal tumours and 22 mixed cases. Metastases were removed mainly by wedge resections, a few lobectomies and pneumonectomy (four cases). One to 72 metastases have been resected per patient, without postoperative deaths and with low morbidity rates.

Osteosarcoma: after chemotherapy in most patients, thoracotomy reveals twice as many metastases as expected. The 5-year survival rate after metastasectomy is 30 per cent.

Soft tissue sarcoma: poor results from chemotherapy allow a very aggressive approach. Up to 20–60 metastases may be resected without added morbidity and with benefit for selected patients.

Melanoma: preoperative evaluation of the number of metastases is usually correct. Mediastinal metastases must be ruled out by mediastinoscopy. The 5-year survival rate is below 20 per cent.

Breast cancer: micrometastases to mediastinal lymph nodes are common. Resectability is assessed by negative mediastinoscopy. Multiorgan spread limits the indications for metastasectomy.

Colorectal carcinoma: few indications for late, solitary metastases in patients with disease-free liver.

Metastasectomy is indicated in a multimodality approach if there is: (1) oncological indication: control of primary tumour, no extrapulmonary metastases (or to be controlled), complete resection predicted, no better treatment; (2) technical resectability without residue and with lung function preserved.

Prognostic factors are the number of metastases, their growth rate, the recent emergence of new deposits and the disease-free interval since control of the primary tumour. Sternotomy is the best choice for bilateral implants.

Results of surgical approach to N_2 lesion in lung cancer: diagnosis and follow-up

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Although, over the years, there has been debate over the efficacy of the surgical treatment of stage IIa lung cancer, our department has always favoured this modality. During a 14-year period, we have treated 338 patients with invasive mediastinal nodes: these comprised 325 men of middle age. Epidermoid cancer was seen in 246 patients (73 per cent), adenocarcinoma in 41 (12 per cent) and undifferentiated in 40 (12 per cent). The neoplastic localization was as follows: 199 in the right lung and 139 in the left lung; the invasive nodes in 59 per cent of patients were subcarinal, in 40 per cent aortic, in 27 per cent paratracheal and in 13 per cent inferior mediastinal. According to the tumour node metastasis (TNM) classification, 175 were T_2N_2 , 114 T_3N_2 and 49 T_4N_2 . The type of resection was pneumonectomy in 40 per cent, lobectomy in 19 per cent and bilobectomy in 5 per cent. In 36 per cent it was possible only to perform exploratory thoracotomy with biopsy. Systematic opening of the mediastinal pleura was performed when lymphadenopathy was present. The complications, both serious and minor, and survival rates are demonstrated in this study: 5-year survival rate was 21 per cent when the tumour was resected, and 6 per cent at 2 years when only exploratory thoracotomy was performed.

Bronchopleural fistula following pulmonary resection in lung cancer: its aetiology and management

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A bronchial fistula usually develops within the third or fourth week after operation. Its main aetiological factor is infection. Pneumonectomy or an upper lobectomy significantly increases the risk of this complication. A bronchial fistula that is large (>7 mm in diameter) and appears within the first month following pulmonary resection can be life-threatening.

We report 42 patients with bronchopleural fistula after pulmonary resection for lung cancer. Among these patients, ten were treated surgically; 11 operations were performed. Five patients underwent resuture or reamputation of the bronchial stump, four had open-window thoracostomy alone, one was treated with open-window thoracostomy and plastic surgery using a pedicled muscle flap, and one had thoracoplasty. The fistula closed completely in 80 per cent (eight of ten) of these cases and the overall mortality was 20 per cent (two of ten).

Thirty-two patients were treated conservatively. In eight patients an alternative method with fibrin sealant for endoscopic control of bronchopleural fistula was also used. In these cases the sealant was applied in combination with cancellous bone fragments to pack the defect in the bronchial stump. In 62 per cent of cases (20 of 32) the fistula closed.

Endoscopic therapy with fibrin sealant for postoperative bronchopleural and gastrointestinal fistulae

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Local or communicating fistulae from the oesophagus, stomach, colon, rectum and bronchus constitute some of the most dreaded postoperative complications. These carry a high mortality rate. Operative approaches have proven to be largely unsatisfactory because of high operative risk and rapid deterioration of the patient's general condition due to infection. Endoscopic techniques to treat these fistulae with fibrin sealant (FS) are thus potentially attractive.

Since 1985, patients with leaking bronchial stumps ($n = 8$) and gastrointestinal fistulae ($n = 13$) after resection were treated endoscopically. The fistulae and their extensions were located by endoscopy combined with radiographic examinations. They were

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then cleaned locally using antiseptic solutions and/or enzymatic drugs. Additionally, sclerotherapy was performed with 2–3 ml 1 per cent Ethoxysclerol injected in small submucosal depots around the fistular orifice to stimulate fibrosis. Finally, occlusion of the fistula was performed endoscopically with 2–5 ml FS using a thin plastic catheter. It was important to apply 500 units ml^{-1} thrombin for rapid clotting of the fibrin plug (within 3 min) and more than 10 000 units ml^{-1} aprotinin to avoid dissolution before the fifth postoperative day. Systemic high-dose antibiotic therapy was given for approximately 7 days.

The fibrin clot in the fistula was replaced in most cases by fresh connective tissue after 5 days. In three patients the endoscopic procedure had to be repeated. All bronchial stumps ($n = 8$) and 11 of 13 gastrointestinal fistulae were closed by granulation tissue by the 14th day. The other two patients underwent operation.

Based on our clinical experience with FS, this simple, effective method should be attempted before operative approaches are considered.

Tissue fibrosis after induction chemotherapy may limit the resectability of lung cancer

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Response to initial chemotherapy may improve resectability of lung cancer. However, tissue dissection after chemotherapy may be difficult. Since 1988, 19 patients treated with one or two courses of chemotherapy had thoracotomy (after negative mediastinoscopy in 15). Two of four small cell tumours and 14 of 15 non-small cell carcinomas were resected (nine squamous, four adenocarcinomas). After complete response, two resections were difficult after three courses and five courses of chemotherapy ($\text{pT}_0\text{N}_0\text{M}_0$) while one resection after three courses was uneventful ($\text{pT}_0\text{N}_1\text{M}_0$). Eleven partial responses and five with no change had necrosis mainly at early surgery (one to three courses) and rarely in late surgery. Fibrosis tended to increase with the number of chemotherapy courses but was not constant. After chemotherapy, necrosis, fibrosis (healing), giant cell granulomas and cholesterol deposits were observed in responding tumours only. Non-tumour sites were not modified. This limited series shows no correlation between fibrosis and the cell type of the primary tumour, or the appearances on computed tomography.

Fibrosis is poorly detected by computed tomography and unpredictable from patient to patient, except by mediastinoscopy after initial N_2 disease. The data reported suggest that surgery should occur within 3 months of induction chemotherapy. Feasibility and resectability should be assessed by mediastinoscopy.

Completion pneumonectomy after bronchial sleeve resection

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During the years 1960–1989, 145 patients underwent complete sleeve lobectomy or sleeve resection of a main bronchus. Follow-up was complete, except for one patient who was lost to follow-up 4 years after operation.

Completion pneumonectomy (CP) was performed in 19 patients (13.1 per cent). Indications were bronchostenosis without malignancy in ten patients, positive resection margins in three, recurrent tumour in five and anastomotic dehiscence in one. Mean (s.d.) age at sleeve operation was 59.3(9.3) (range 27–71) years.

Histology revealed squamous cell carcinoma in 18 patients and carcinoid tumour in one. In the five patients with recurrent tumour, four had negative resection margins and one, carcinoma *in situ* at the initial operation. Mean interval between sleeve resection and CP was 5.7 (range 3–16) months in the patients with stenosis and 6.6 (range 1–17) months in the others.

There were three postoperative deaths (15.8 per cent), two due to cardiac causes and one due to fistula of the bronchial stump.

Mean follow-up was 53.2 months. Five- and 10-year survival rates after CP for the patients with stenosis were 63 and 47 per cent and for the others 52 and 52 per cent, respectively.

Close follow-up after sleeve resection with repeat bronchoscopies is necessary to detect early recurrent cancer or bronchostenosis and to treat appropriately.

Experimental electron microscope study of lung preservation

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The experiments were carried out on Mini-LEWE pigs. The heart and lung were removed *en bloc* from the chest. In one group, modified Euro-Collins solution was used for perfusion at 4°C, and in the second group University of Wisconsin (UW) solution at 10°C was used. The trachea was clamped when the lung was inflated up to 50 per cent with oxygen. The perfusion solution was infused into the main pulmonary artery at a rate of 20 $\text{ml kg}^{-1} \text{min}^{-1}$, at a maximal pressure of 10 mmHg. As soon as infusion was finished, the tip of the left atrial appendage was excised to allow free drainage of the infusate after it had passed through the lungs. The organs were stored for 4 h in cold perfusion solution, then the left lung was transplanted to a recipient animal.

Material for electron microscopy was removed before perfusion started, after blood-free perfusion, each hour during storage, during reperfusion after transplantation, and then by open lung biopsy hourly up to 10 h and also at 24 h after transplantation.

Transmission electron microscopy of lungs preserved in Euro-Collins solution demonstrated sensitivity of the alveolar membrane to high perfusion pressure, with swelling of mitochondria, microsomes, Golgi apparatus and endoplasmic reticulum of the pneumocytes. There was more fluid in the extracellular space using this solution. Both agents effectively preserved the bronchiolar epithelium. The lungs preserved in UW solution were ultrastructurally more normal 24 h after transplantation than the lungs preserved in Euro-Collins solution.

These results suggest that UW solution should be considered for lung preservation in clinical transplantation.

Bronchial revascularization in experimental lung transplantation

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This study assesses different methods of bronchial anastomosis in lung transplantation.

Fifteen unilateral left lung transplantation procedures were performed in dogs. Three techniques were used to perform the bronchial anastomoses: (1) reinforcement with omentum; (2) telescoping of the donor bronchus in the recipient; and (3) telescoping plus omentum. Clinical assessment of the animals and histology of the bronchial anastomoses were performed 15 days after the procedure. Bronchial anastomotic segments were sectioned for light microscopic quantitative assessment of viability, scored from 0 to 9 (0, normal; 9, necrotic). To compare groups, a Newman–Keuls test was employed.

There were no anastomotic leaks in any group. The total histology scores were 12 for the first procedure, 34 for the second and ten for the third. There was a significant improvement in viability in the first and third procedures ($P = 0.05$) compared with telescoping alone.

We conclude that omentum promotes revascularization of the donor bronchus. Moreover, telescoping may offer some mechanical protection of the bronchial anastomosis. The methods complement each other and could together provide optimal protection to the bronchial anastomosis in lung transplantation.

Radioiodine treatment of pulmonary metastases of thyroid cancer: prognostic criteria of response

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In the period 1980–1990, 23 patients with pulmonary metastases (PM) from differentiated thyroid cancer were treated with iodine-131. They represented 6.3 per cent of all patients with thyroid cancer treated during that period and 21 per cent of patients with locally advanced tumours. A mean dose of 13–14 GBq radiolabelled iodine-131 was given in four to five fractions over 2–4 years. The

tumour node metastases classification and age were found to be the most important factors for metastasis. The most favourable 7–8-year disease-free period for five patients was achieved in those aged 7–40 years.

In the high-risk group (pT₃₋₄pN_{1a-1b}) a diagnosis of PM was established early after 340 MBq high tracer activity and the treatment started after thyroidectomy and ablation. In the oldest group of eight patients (over 60 years), even after 28 GBq iodine-131 PM still showed uptake, but the patients survived more than 5 years with tumours and had an excellent quality of life. Multiple bone lesions with PM worsened the prognosis and two patients died within 1 year. Single bone metastases (vertebra and rib) with PM did not change the prognosis.

Serum levels of carcinoembryonic antigen, sialic acid and neurone-specific enolase in lung cancer

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We report the follow-up of 70 patients with lung cancer, including 48 with squamous carcinoma (69 per cent), 12 with adenocarcinoma (17 per cent) five with oat-cell tumours (7 per cent) and five with adenosquamous tumours (7 per cent). In addition to other studies, they were analysed for carcinoembryonic antigen (CEA), sialic acid and neurone-specific enolase (NSE) before surgery, immediately after surgery and at 3-month intervals.

Sialic acid is an extremely sensitive but non-specific indicator, varying from 100 per cent in adenosquamous tumours to 50 per cent in adenocarcinomas. Before surgery, tumour typology was 60 per cent positive in squamous carcinoma, 50 per cent in adenocarcinoma, 60 per cent in oat-cell tumours and 100 per cent in adenosquamous tumours. CEA showed a great fluctuation according to the tumour type, being negative in oat-cell tumours, present in 25 per cent of squamous carcinomas and positive in about 60 per cent of adenocarcinomas and adenosquamous tumours, indicating well differentiated cellular origins. A similar conclusion can be drawn about the cellular type of the tumour related to NSE, which showed positive indicators in 20 per cent of squamous carcinomas, adenocarcinomas and adenosquamous carcinomas, but in 80 per cent of oat-cell tumours.

From these results we conclude that the evolution and therapy of patients with cancer may be monitored by a common indicator, such as sialic acid, and differential markers such as CEA in adenosquamous cancer and NSE in oat-cell tumours.

Genital origin of lung metastases

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Because of abundant cardiac flow and lymph connections, the lung is often the site of metastasis. The author's opinion is that the Müllerian system extends by lymphatic channels to the pleura and the lung. Two cases of multifocal neoplasia extending by this route are reported. Pseudomeigs peritoneopleural effusion is frequently seen in the third stage of ovarian cancer, especially on the right side (30 per cent).

Blood-borne metastases were found in 15 cases of germ cell neoplasia and 30 cases of trophoblastic disease. The incidence of genital metastatic disease, especially trophoblastic disease, has risen since the Chernobyl accident. Radical surgery and/or chemotherapy is the treatment of choice. Hormonal treatment is recommended in receptor-positive primary tumours. Müllerian carcinomas metastasize like endometrial and endometrioid neoplasias. In three cases pulmonary metastases have been the first presentation of low-grade ovarian malignancies.

Indications for and results of sympathectomy and vagotomy by thoracoscopy

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Since 1959 2653 transpleural neurotomies by thoracoscopy have been performed by the author according to the directions of Kux¹. The primary indications such as hyperhidrosis of the head and hands as well as duodenal ulcer have been extended to erythrophobia, Sudeck's syndrome, Raynaud's disease, migraine, causalgias of the arm and spastic bronchial asthma.

In a study of 1200 patients operated on by the author from 1963 to 1975, Enggist found in 381 hyperhidrotics 91 per cent cured, 7 per cent improvement and 2 per cent failure. The Raynaud's syndrome group (210 cases) has shown 25 per cent cured, 39 per cent improvement and in 36 per cent only temporary success. The migraine group (184 cases) demonstrated 18 per cent healing, 48 per cent improvement and in 34 per cent poor results.

The risks of the intervention are minimal. Possible complications are bleeding, air embolism, heart failure, pneumonia, lesions of recurrent nerve and thoracic duct. In the past 29 years, however, the only serious incident that occurred was bleeding of an intercostal artery, requiring thoracotomy. No deaths occurred. The results of the method are satisfactory, and for hyperhidrosis are excellent.

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Rat liver transplantation: an improved model including arterial reconstruction and simplified suture techniques

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Methods of rat liver transplantation include cuff anastomoses in the recipient operation or conventional microsurgical suture techniques. These methods do not provide for reconstruction of the arterial blood supply to the liver. The present method adheres to the principle of microvascular suture technique and includes rearterialization of the transplant.

During the donor operation the organ was prepared with an arterial pedicle including the aortic origin of the coeliac trunk. The liver was flushed *in situ* simultaneously via the portal vein and the hepatic artery. The implantation of the donor organ into the recipient site was accomplished with simplified suture techniques with respect to venous anastomoses. Rearterialization of the liver was carried out by means of a cuff technique. A choledochcholedochostomy with a splint technique and additional suturing was performed for anastomosis of the bile duct.

With practice, an anhepatic phase of about 20 min was achieved, which is below the critical 30-min limit for survival. Our most recent perioperative mortality rate is up to about 9 per cent ($n = 180$).

This improved rat liver transplantation model, including simplified microvascular suture techniques and arterial reconstruction, has proved to be valuable for investigations on organ ischaemia, preservation and reperfusion. Since suture techniques are used instead of cuff techniques for the venous anastomoses, there is no need for additional *ex situ* preparation of the donor liver. The combination of portal and arterial *in situ* perfusion in the donor operation and rearterialization of the transplant in the recipient operation allows for more accurate reproduction of the clinical conditions.

New technique for the collection of pancreatic juice from pancreas allografts in rats

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It has been suggested that monitoring of biochemical markers such as amylase activity in the pancreatic juice may contribute to early detection of acute rejection in clinical pancreatic transplantation. To evaluate the usefulness of these biochemical markers for detection of acute rejection, a rat model was developed in which pancreatic juice could be collected continuously and safely from pancreatic grafts.

The pancreas was grafted in the recipient's abdomen by two vascular anastomoses. The graft's bile duct was cannulated by a silicon tube and the outlet of the pancreatic duct was ligated to achieve external drainage. The cannula ran subcutaneously to the back of the rat's head where it was connected with the collecting system, which included a swivel to allow free movement of the animal. To prevent dehydration and metabolic acidosis owing to loss of pancreatic juice, this was reintroduced to the rat's body through a second cannula connected to the graft duodenum. Volume and pH of pancreatic juice and amylase production were assessed daily up to 8 days after operation. Two groups, BN-LEW allografts and LEW-LEW isografts were compared; none of the rats received immunosuppressive treatment.

The volume and pH of the pancreatic juice and the amylase production in the allografts increased from day 1 after transplantation to reach a maximum on day 4. However, on day 6 following transplantation, the volume, pH and amylase production decreased sharply. This decrease correlated well with histological signs of progressive acute pancreas rejection. Isografts showed a similar increase in juice volume, pH and amylase production to the allografts in the days immediately after transplantation. In contrast to allografts, these values remained stable up to day 8 after transplantation, the last sampling point. None of the isografts showed histopathological signs of rejection.

This new technique can be used for the daily collection of pancreatic juice after pancreas transplantation in rats and might be helpful in detecting markers for the early diagnosis of pancreas allograft rejection.

Combined pancreas and kidney allotransplantation in the pig

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A model of *en bloc* simultaneous pancreas and kidney transplantation has been established which decreases preservation time, operating time and clamp time. The method was developed on 32 Yorkshire pigs, with the following technique: the donor aorta (with coeliac axis, superior mesenteric artery and left renal artery) is anastomosed *en bloc* to the recipient's aorta in a side-to-oblique fashion. The portal vein is anastomosed end-to-side to the distal vena cava, and the left renal vein end-to-side to the left common iliac vein. The donor duodenum is anastomosed to the bladder to allow monitoring of urinary amylase concentration for rejection.

The proposed technique facilitates the vascular reconstruction, saving one arterial anastomosis, and additionally saves about 50 min of operating and clamp time. None of our recipients has died from a technical complication. The pig is a large animal suitable for experimental pancreatic transplantation by virtue of its anatomy and transplant immunology, both of which are similar to those of humans.

In conclusion, this technique could be used in humans, especially in adult uraemic diabetic patients who receive a combined pancreas-kidney allotransplant from a paediatric cadaver donor.

Use of the 5'-nucleotidase assay in the assessment of preservation injury in cold-stored dog liver grafts

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The activity and localization of the plasma membrane bound enzyme 5'-nucleotidase (5'-NT) in liver tissue are sensitive parameters of ischaemic damage. 5'-NT activity was demonstrated histochemically in cryostat sections of liver tissue using the lead salt method. In this study, the 5'-NT assay was used to assess graft viability in cold-preserved dog livers. First, the 5'-NT assay was applied in relation to graft function in orthotopic liver transplantation experiments in dogs. Second, an *in vitro* method was devised with which the efficacy of two preservation solutions could be compared in one dog liver.

Twelve dog livers were flushed *in situ* with cold University of Wisconsin (UW) solution and stored for 24 h, 48 h or 72 h before orthotopic transplantation. Graft function was determined by survival of the recipient dog and peak serum glutamic-oxaloacetic transaminase levels. All dogs with liver grafts preserved for 24 h ($n = 4$) or 48 h ($n = 3$) survived (>5 days). Pretransplant 5'-NT scores ranged from 61 to 100 per cent. The livers preserved for 72 h ($n = 5$) did not show life-supporting function. Pretransplant 5'-NT scores (33 per cent, $n = 5$) were significantly lower in this group ($P < 0.05$).

In the second experiment comprising six dogs, the main right and left branches of the portal vein were cannulated and flushed separately *in situ* with cold UW solution or EuroCollins (EC) solution. After hepatectomy, the right and left liver lobes were split and stored at 4°C in either solution. Sequential biopsies were taken after 24 h, 48 h and 72 h storage time. After 48 h storage in EC, the 5'-NT score had decreased to 31 per cent ($n = 6$), whereas in UW, 5'-NT score was 76 per cent ($n = 6$). Significantly higher 5'-NT scores were found also after 24 h and 72 h preservation in UW ($P < 0.05$). This result is in keeping with the higher preservation tolerance of liver grafts preserved in UW.

The 5'-NT assay provides a simple and rapid method of testing the viability of liver grafts *in vitro*. It can also be used to test solutions for liver preservation.

Homologous testis transplantation in dogs

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There is growing interest in the possible use of homologous testis transplantation for the treatment of anorchia and male infertility. In order to test further the surgical and immunological feasibility of this therapy, two series of experimental studies of homologous testis transplantation have been carried out in dogs. In the first, four Beagle brothers were transplanted using microsurgical techniques for end-to-end anastomosis of the testicular vessels and the vas deferens. All animals received cyclosporin therapy for 3 months after the operation. The longest functional survival of the grafts in this series was 5 months. A second series of operations was performed on ten mongrel dogs. The same surgical technique was employed and the animals were randomized into three groups. Group 1 received no immunosuppression, group 2 received cyclosporin alone and group 3 cyclosporin and prednisolone. The median graft survival time in this study was 18 days, significantly less than in the first study (71 days). The animals in group 3, however, had three times longer graft survival times than those in the other two groups. The results of these two studies indicate that long-term survival of a homologously transplanted testis graft is possible and future research in this field is required.

Effects of the prostacyclin analogue ZK 36374 and lipoxigenase inhibitor NDGA on ischaemia-reperfusion injury in rat liver

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In this study, the effects of iloprost (ZK 36374) and nordihydroguaiaretic acid (NDGA) on warm ischaemia and reperfusion injury in the rat liver were investigated. The portal and hepatic arterial flow to the left and median lobe of the liver was interrupted selectively for 1 h. Rats were given isotonic saline ($n = 12$, group I), iloprost $25 \mu\text{g kg}^{-1}$ intravenously ($n = 12$, group II) just before warm ischaemia or NDGA $10 \mu\text{g kg}^{-1}$ intravenously ($n = 12$, group III) 5 min before reperfusion or the same drugs were given together ($n = 12$, group IV). Aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) and lactate dehydrogenase (LDH) levels were determined before ischaemia and 5 min, 2 h, 2 days and 7 days after reperfusion. Tissue malonaldehyde (MDA) and glutathione (GSH) levels were determined 5 min, 2 days and 7 days after ischaemia-reperfusion injury. Histopathological examination of the liver was carried out by light microscopy.

The serum ASAT, ALAT and LDH levels improved significantly in groups II, III and IV, compared with group I ($P < 0.05$). Iloprost and NDGA did not exert an additive effect. There was a significant decrease ($P < 0.05$) in tissue MDA levels and a significant increase ($P < 0.05$) in tissue GSH levels in groups II and III compared with groups I and IV. The values did not differ significantly in group IV compared with group I.

In conclusion, iloprost and NDGA were found to be beneficial in preventing the ischaemia-reperfusion injury in the rat livers. The loss of the beneficial effect when both drugs were given together was related to the partial cyclo-oxygenase inhibitor effect of NDGA.

Sandostatin protects against endotoxin-induced liver and kidney necrosis and impairment of renal function

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Previous studies have demonstrated that Sandostatin (SMS) ameliorates hepatic necrosis and renal tubular damage following *Escherichia coli* endotoxin administration in rats. The aim of the present study was to establish whether the beneficial effects of SMS on the liver and kidney could be explained by alterations in blood flow to these two organs.

Groups of male Wistar rats ($n = 10$) received either intraperitoneal endotoxin ($2 \text{ mg } 100 \text{ g}^{-1}$) or saline. A further group received SMS immediately before and 12 h after administration of endotoxin. Hepatic and renal blood flow were measured by the microsphere method and renal function was assessed by plasma clearance of Mag3, a renal tubular agent. SMS prevented the hepatic necrosis and renal tubular damage observed in rats treated with endotoxin alone. Cardiac output was significantly reduced in the two groups that received endotoxin ($P < 0.001$ versus control group, ANOVA). There was no significant difference in hepatic or renal blood flow between the groups. Mean (s.e.m.) Mag3 clearance was significantly reduced in the group that received endotoxin ($0.76(0.05) \text{ ml min}^{-1} 100 \text{ g}^{-1}$) compared with controls ($1.11(0.09) \text{ ml min}^{-1} 100 \text{ g}^{-1}$) and SMS-treated animals ($1.23(0.09) \text{ ml min}^{-1} 100 \text{ g}^{-1}$).

Endotoxaemic hepatic necrosis and renal tubular damage appears to result from a direct effect on the liver and kidney rather than from alterations in haemodynamics. Renal tubular function is protected by previous administration of SMS, although the precise mode of action is not clear.

Protective role of verapamil and iloprost in ischaemia-reperfusion-induced renal injury

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The cytoprotective effects of verapamil and iloprost (ZK 36374) have been investigated in Wistar albino rat kidneys subjected to 60 min of warm ischaemia-reperfusion. The rats were anaesthetized with ether and the renal artery and vein were clamped after giving 80 units heparin and 10 ml kg^{-1} isotonic saline with or without medication through the internal jugular vein, and the abdomen was closed. After 60 min of ischaemia, rats were reanaesthetized and the clamp was freed. The study groups were as follows: group A, sham ($n = 6$); group B, ischaemia untreated ($n = 24$); group C, verapamil 0.3 mg kg^{-1} ($n = 15$); group D, iloprost $25 \mu\text{g kg}^{-1}$ ($n = 12$); and group E, verapamil + iloprost ($n = 12$). Six rats from each group were killed 5 min after reperfusion for the determination of tissue reduced glutathione (GSH) levels. The 7-day survival of all the treated groups was significantly better ($P < 0.05$) than the ischaemia untreated group (group B, 61.1 per cent; group C, 88.8 per cent; all others, 100 per cent). The mean (s.d.) serum creatinine levels on day 3 were significantly lower ($P < 0.01$) in group E ($0.72(0.09) \text{ mg dl}^{-1}$) compared with group B ($1.41(1.08) \text{ mg dl}^{-1}$) and they were significantly lower ($P < 0.05$) in group E ($0.66(0.08) \text{ mg dl}^{-1}$) than in group B ($1.07(0.46) \text{ mg dl}^{-1}$), group C ($0.98(0.22) \text{ mg dl}^{-1}$) and group D ($0.82(0.1) \text{ mg dl}^{-1}$) on day 7. The tissue GSH levels of the kidneys sampled immediately after the reperfusion were significantly lower in group B than in all other groups.

These results indicate that although verapamil and iloprost have independent cytoprotective effects on ischaemia-reperfusion injury of the rat kidney, the protection afforded when both drugs are combined is synergistic, that the mechanism of potentiation of cytoprotection is not limited to the oxygen free radical-induced effects on cells and an almost complete protection can be obtained by such an intervention.

Effects of verapamil and *Ginkgo biloba* extract in the prevention of warm ischaemia-induced acute renal failure in dogs

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Our study was undertaken to evaluate the efficacy of verapamil and *Ginkgo biloba* extract in the prevention of warm ischaemia-induced acute renal failure following renal autotransplantation in the dog.

Eighteen dogs, six controls, six verapamil- and six *Ginkgo biloba*-treated, were randomly selected. The first group received no medical therapy before the warm ischaemia of 60 min. The second group was given verapamil at 0.3 mg kg^{-1} (intra-arterially); the third group was given *Ginkgo biloba* extract at 50 mg kg^{-1} (intravenously) before the ischaemia. After all these procedures, the left kidney was grafted to the right iliac fossa in the warm ischaemic period and then contralateral nephrectomy was performed. The dogs were followed

Transplantation

for 48 h. Creatinine was measured serially and histopathology of the autograft was examined.

In the control group, four had severe renal insufficiency and two mild renal insufficiency. In the group receiving *Ginkgo biloba* extract, two had severe renal insufficiency, one moderate renal insufficiency and three mild renal insufficiency. In the group receiving verapamil, one had severe renal insufficiency and three mild renal insufficiency.

The mean creatinine level was 176 mmol l^{-1} in the control group; 163 mmol l^{-1} in the *Ginkgo biloba*-treated group; 156 mmol l^{-1} in the verapamil-treated group. The difference in distribution of creatinine between the groups was statistically significant (unpaired two-tailed *t* test, $P < 0.05$).

Liver graft assessment in organ donors by the lidocaine monoethylglycinexylidide test is unreliable

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The lidocaine monoethylglycinexylidide (MEGX) test was performed in 38 liver donors before organ harvesting. The serum MEGX 15 min after an intravenous bolus of 1 mg kg^{-1} lidocaine in the donor (MEGX t_{15}) was correlated retrospectively with outcome of the transplant and early liver graft function. Three donors were excluded from the study because of pretest contamination with lidocaine. Among the remaining 35 orthotopic liver transplants (OLTs), four patients were retransplanted within 10 days post-OLT (primary non-function (PNF): $n = 4$; early severe graft dysfunction: $n = 2$), and three recipients died, with median (range) donor MEGX t_{15} (ng ml^{-1}) of 100 (86–119) and 169 (146–182), respectively, when compared with 87 (18–245) in the remaining 28 OLT patients alive with functioning grafts. Considering the literature¹, a MEGX t_{15} value less or more than 80 ng ml^{-1} was considered arbitrarily as the cut-off point which may predict poor or good liver graft quality, respectively. Donor and preservation data were not statistically different in the two corresponding groups in terms of mean donor age (21.9 versus 21.0 years), days in intensive care unit (2.8 versus 2.6), ischaemic time in hours (13.6 versus 12.7) and T cell crossmatch. One-month graft survival rate was significantly higher in the $<80 \text{ ng ml}^{-1}$ group (12 of 12; 100 per cent) when compared with the $>80 \text{ ng ml}^{-1}$ group (16 of 23; 70 per cent; $P = 0.036$). Moreover, early (days 1–5) post-OLT cytolytic and functional parameters were similar in both groups: peak serum glutamic-oxaloacetic transaminase (SGOT) (units l^{-1}) (mean(s.d.): 2356(2622) versus 2173(3036), P not significant), peak serum glutamic-pyruvic transaminase (SGPT) (units l^{-1}) (1684(1476) versus 1952(1939), P not significant), mean SGPT (1051(791) versus 1354(1533), P not significant), minimum prothrombin time (per cent) (43(17) versus 43(13), P not significant), and peak total bilirubin (mg dl^{-1}) (9.8(4.9) versus 10.6(5.0), P not significant). In conclusion: (1) the MEGX test failed to predict graft outcome, as the two PNF cases had 'excellent' MEGX t_{15} ; (2) low donor MEGX t_{15} correlated neither with poor graft outcome nor with early liver dysfunction. Low MEGX t_{15} value should thus not preclude the use of a liver donor, particularly in the current context of organ shortage.

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Cyclosporin A versus OKT3 after orthotopic liver transplantation

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The aim of this study was to compare two different immunoprophylactic protocols in 36 consecutive patients undergoing orthotopic liver transplantation: group I ($n = 19$) received cyclosporin A, prednisone and azathioprine, group II ($n = 17$) received OKT3, prednisone and azathioprine. We analysed cardiorespiratory disorders, incidence of rejection, infections, postoperative mortality (2 months) and liver and renal function tests. The results are summarized in the Table.

	Group I	Group II
Respiratory distress	21	23
Acute rejection by 15th day	42	17*
Acute rejection by 30th day	47	23
Acute rejection by 60th day	63	23*
Major infections	79	47*
Renal failure	37	0*
Mortality rate	15.7	5.8

Values are percentages. * $P < 0.05$ versus group I

Plasma bilirubin ($P < 0.01$) and creatinine ($P < 0.05$) levels were significantly lower in patients treated with OKT3 during the early postoperative period.

It is concluded that OKT3 reduces the incidence of rejection, infections and renal failure after orthotopic liver transplantation. Liver function after transplantation recovers earlier in patients treated with OKT3.

Reoperations for biliary tract complications following orthotopic liver transplantation

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The aim of this study was to analyse biliary tract complications after orthotopic liver transplantation in a new liver transplant centre.

During a 2-year period we have performed a total of 48 liver transplantations in 46 patients. Biliary tract reconstruction consisted of a choledochocholedochostomy over a T tube in 41 cases and a Roux limb choledochojejunostomy in seven (two with sclerosing cholangitis, four having repeat transplants and one with secondary biliary cirrhosis). The T tube was removed between 12 and 16 weeks after operation in all but two patients, in whom the tube was removed 2 and 3 weeks after operation.

There was no intraoperative mortality. During the first 2 postoperative months, four patients died (9 per cent), none because of biliary complications. After a follow-up of 8 (range 2–27) months the survival rate of patients was 85 per cent (41 of 48). A total of nine biliary complications (20 per cent) was documented and seven of these patients required further surgery (15 per cent). During the early postoperative period four patients had a bile leak; three had an anastomotic leak (one underwent reoperation and two had ultrasonographically guided drainage) and one had T tube dislodgement with leak (reoperation was performed). Four patients developed biliary peritonitis after T tube removal and reoperation was required in each case. Finally, one patient suffered a hilar biloma cavity after a hepatic artery thrombosis.

In conclusion, we stress the low incidence of reoperations for early biliary complications (two patients) and the high incidence of biliary peritonitis after T tube removal (four of 41 patients; 10 per cent).

Visceral leishmaniasis: an unusual cause of persistent splenomegaly after orthotopic liver transplantation

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A 50-year-old female liver transplant recipient presented with pancytopenia, huge splenomegaly and intermittent low grade fever 1 year after transplantation. Doppler ultrasonography showed patent portal and splenic veins; transcutaneous liver biopsy showed no rejection phenomena but rather a graft infection with *Leishmania*. Active infection was confirmed by positive cultures for *Leishmania* serology. As the patient had never resided outside Switzerland, the infection probably originated from the donor liver. We report, therefore, for the first time the occurrence of visceral leishmaniasis in a patient who has received an orthotopic liver transplant. If splenomegaly persists during the late postoperative period, unusual protozoal infections such as leishmaniasis must be considered.

Hepatic isoenzymes of alkaline phosphatase as a complementary marker of early rejection in liver transplantation

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This study evaluates whether a serum profile of alkaline phosphatase isoenzymes could be used to diagnose rejection and infection and to distinguish between these in 12 patients undergoing orthotopic liver transplantation.

Alkaline phosphatase isoenzymes were determined by a gel agarose technique (Paragon-Isopal-Beckman). Complementary methodology such as inactivation by heat and neuraminidase were also used.

All patients showed a significant increase in total alkaline phosphatase (EC 3.1.3.1) ($P < 0.001$) with an isoenzymatic pattern, increase in hepatic and macro fractions and reduction in bone isoenzymes ($P < 0.001$). In cases of rejection there was a significant increase ($P < 0.001$) in hepatic isoenzymes and in cases of infection or other complications a large increase in macro isoenzymes was found.

We conclude that the changes in the profile of alkaline phosphatase isoenzymes are markers of acute rejection. We are continuing to explore the fundamental mechanism underlying our observations.

Case against recurrence of primary sclerosing cholangitis and primary biliary cirrhosis after liver transplantation

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A 40-year-old man underwent hepatic transplantation in 1984 because of primary sclerosing cholangitis (PSC). Cholangiography obtained 6 months later because of an obstructive liver enzyme profile showed changes compatible with the primary disease. The patient underwent retransplantation 5 years later; during operation a very short Roux-en-Y limb was found. Regurgitation of food was responsible for the severe cholangitic changes.

A 36-year-old woman was transplanted in 1980 because of end-stage primary biliary cirrhosis (PBC). Nine years later retransplantation was necessary because of severe cholestatic disease although this patient had been included recently in a series of patients presenting as 'recurrent PBC'. Pathological examination of the first allograft was compatible with late chronic rejection and not with recurrent disease.

PSC and PBC have been thought possibly to recur after transplantation. Complete and long-term follow-up in both case reports argue against recurrent disease. Furthermore, both case reports clearly stress the necessity for complete follow-up to avoid false conclusions.

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Adult liver transplantation: experience with 247 grafts in 212 recipients

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During the period February 1984 to November 1991, 560 liver transplantations (LTs), were performed at this institution; 247 LTs were done in 212 adults. Of these, 182 patients (85.8 per cent) had benign cholestatic (42 of 182 patients; 19.8 per cent) or hepatocellular (140 of 182 patients; 66 per cent) liver disease. Thirty patients (14.2 per cent) were transplanted for malignant primary (24; 11.3 per cent) or secondary (six; 2.8 per cent) liver disease. Urgent LT was necessary in 40 patients (18.9 per cent); 20 and seven of these patients

respectively presented with a fulminant and subfulminant liver failure. Operative and hospital mortality rate was 20.8 per cent for the whole group; 23.1 per cent (42 of 182 patients) for the benign and 7 per cent (two of 30) for the malignant liver disease group. Nearly all perioperative deaths were from haemorrhagic and/or septic complications. Late mortality rate, defined as death after hospital discharge, reached 9.4 per cent (20 of 212 patients) and was related mainly to recurrent disease, e.g. hepatitis B infection (three patients) and cancer (nine patients). A total of 29 patients (13.7 per cent) had 32 retransplantations (re-LTs). Indications for re-LT were 'early' non-function (13 of 32 re-LT; 40.6 per cent), acute (nine of 32; 28 per cent) and chronic rejection (six of 32; 18.8 per cent), recurrent hepatitis B (two of 32; 6.3 per cent) and hepatic artery thrombosis (two of 32; 6.3 per cent). Eleven patients (38 per cent) died shortly after re-LT. Survival after re-LT is 48.3 per cent (14 of 29 patients). At closure of the study survival for the whole group was 69.8 per cent (148 of 212 patients). There were no major differences between survival rates in elective (121 of 172 patients; 70.2 per cent), urgent (27 of 40 patients; 67 per cent) and subfulminant failure (19 of 27 patients; 70 per cent) patient groups. There was, however, a steady lowering of perioperative mortality rate to 14 per cent (11 of 78 patients) in 1990-1991 from 25 per cent (34 of 137 patients) in 1984-1989 and improvement of survival in the subfulminant liver failure group (91 per cent (ten of 11 patients) in 1990-1991 versus 56 per cent (nine of 16 patients) in 1984-1989). The review of this larger transplant series confirms that LT remains a demanding surgical and medical undertaking. Results can be further improved by taking into account more appropriate patient selection, better immunosuppression and improved perioperative care.

Arteriovenous fistulae after kidney allograft biopsy

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Arteriovenous fistula is a well known but rarely diagnosed complication of percutaneous biopsy of renal allografts. In the past, diagnosis was usually made when clinical signs occurred. Echo Doppler devices have made non-invasive diagnosis of these fistulae possible.

Echo Doppler examinations of renal allografts were performed after 75 biopsies in 70 patients who had undergone transplantation in this centre since April 1990. A total of ten arteriovenous fistulae was diagnosed within 1 week of biopsy. Repeated echo Doppler examinations were performed in all patients at least 2 months later, but no additional fistulae were detected. All fistulae were detected by abnormal colour shading of the artery and vein of the fistula due to high blood velocity. Quantification of these velocities in the artery supplying the fistula showed higher systolic velocities (mean (range) 58 (25-111) cm s^{-1}) compared with velocities in a normal artery of similar size and location in the graft (mean (range) 38 (20-65) cm s^{-1}). Diastolic velocities differed even more (mean (range) 32 (9-72) cm s^{-1}) in the artery supplying the fistula compared with diastolic velocities in a normal artery (mean (range) 7 (0-13) cm s^{-1}). The difference in resistance index between the different arteries ranged from 0.15 to 0.53 (mean 0.36). After detection of fistula, four of the grafts were lost owing to untreatable rejection. Of the remaining six fistulae, one disappeared spontaneously and the other five persisted and showed increasing blood velocities. None of these fistulae, however, has had an impact on renal function necessitating intervention.

In conclusion, arteriovenous fistulae are a frequent complication after renal allograft biopsy, but seldom jeopardize renal function. Detection and monitoring can readily be performed by echo Doppler examination.

Kidney retrieval from non-heartbeating donors: a controlled study of transplantation results

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To overcome the shortage of kidneys available for transplantation, kidneys from non-heartbeating donors (non-HBD) have been investigated. These comprised 25 per cent of all kidney grafts in our programme. This study reviews our results with 34 kidneys from

non-HBD, of a total of 482 transplanted kidneys from 1985 to 1991, compared with 34 control kidneys from heartbeating donors (HBD) matched for age, sex, primary graft or retransplant and transplantation year. Cold ischaemia time, preservation solutions used, preoperative dialysis, number of HLA mismatches and serum antibody levels did not differ statistically between the two groups. Only the last hour diuresis of the donors in the non-HBD group was significantly lower and their creatinine levels significantly higher than the HBD group. Sixteen of the HBD group died from head injuries, two from cerebrovascular aneurysms and one from asphyxia. Triple immunosuppressive therapy (methylprednisolone, azathioprine, cyclosporin A) was used for HBD and for nine non-HBD recipients transplanted before 1986. Since then, initial cyclosporin A in the non-HBD group has been replaced by intravenous antithymocyte globulin for about 10 days.

	HBD group (n = 34)	Non-HBD group (n = 34)	F
Primary non-function	1 (3)	3 (9)	0.26
Temporary postoperative dialysis	10 (29)	17 (50)	0.13
Serum creatinine at 1 week ($\mu\text{mol l}^{-1}$)	185	223	0.98
Serum creatinine at 1 month ($\mu\text{mol l}^{-1}$)	154	165	0.65
Serum creatinine at 1 year ($\mu\text{mol l}^{-1}$)	152	147	0.52
1-Year patient survival (%)	89	78	>0.05
1-Year graft survival (%)	85	76	>0.05

Values in parentheses are percentages

Six of 34 (18 per cent) kidneys in the non-HBD group (five retransplants) showed vascular rejection, five of them associated with haemolytic uraemic syndrome (HUS); two of these six kidneys recovered, four failed (two with primary non-function). Four of six cases with HUS had initial cyclosporin A according to our former protocol. In the HBD group no HUS was observed. The study shows that good short- and long-term results can be achieved with kidneys from non-HBD. While the reason for acute vascular rejection associated with HUS in retransplanted patients is not clear, we propose to use kidneys from non-HBD subjects in the future for first transplants only and to avoid cyclosporin A as initial immunosuppression. We conclude that organ retrieval from non-HBD is an adequate approach to a donor source that could significantly increase the number of kidney grafts in most transplantation programmes.

Recipient nephrectomy for urinary infection after renal transplantation

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Bilateral recipient nephrectomy after renal transplantation can reduce the frequency of urinary infection. In this retrospective study, patients who underwent recipient nephrectomy after renal transplantation between 1982 and 1990 were reviewed. In 12 cases this was for recurring urinary infection thought to be arising from native kidneys. The causes of end-stage renal failure were chronic pyelonephritis in ten, drug-induced nephropathy in one and hypoplastic kidney in one. There were ten women and two men, with a mean age of 25 years. The mean length of time between transplant and recipient nephrectomy was 25.7 months. The mean number of infections per graft year was three before nephrectomy, with mean follow-up period of 32 months. The Table shows the frequency of infection after nephrectomy.

Patients (n)	Infections (total no.)	Follow-up (months)	Infection frequency after nephrectomy
3	0	48	0
3	3	77	1 in 25 months
1	4	70	1 in 17 months
2	4	44	1 in 11 months
1	3	30	1 in 10 months
1	5	35	1 in 7 months
1	13	79	1 in 6 months

These results show that frequency of infection was reduced in over one-half of these patients, with complete cure in 25 per cent. We believe that bilateral recipient nephrectomy is useful in selected patients where antibiotics have failed.

Dysphagia after renal transplantation

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Dysphagia after renal transplantation is rare and this prompts us to report on five patients under our care.

Since cyclosporin was included in our immunosuppressive protocol in August 1983, 224 transplants have been performed in Lausanne up to November 1991. A retrospective review revealed five patients who developed dysphagia during, or shortly after, anti-rejection therapy with high doses of methylprednisolone. In four cases, monoclonal or polyclonal antilymphocyte globulins were also injected. All patients were investigated by upper gastrointestinal endoscopy with biopsies, and herpetic oesophagitis was diagnosed in all cases. Treatment by intravenous acyclovir combined with a reduction in immunosuppressive drugs was successful. The five patients were discharged with functioning grafts.

We conclude that dysphagia in a transplant recipient may be an early sign of an opportunistic infection induced by immunosuppression.

Successful renal transplantation with kidneys from asystolic donors maintained under extracorporeal cardiopulmonary bypass

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The aim of this study was to compare the fate of kidneys transplanted from non-heart-beating donors (NHBD) with that of kidneys harvested from heart-beating donors (HBD). In the NHBD group, warm ischaemia time was reduced by initiating total body cooling with extracorporeal cardiopulmonary bypass immediately after diagnosis of death. Increasing the safe period in this way, there is enough time to obtain permission for organ retrieval. Between November 1989 and November 1991, a total of 96 kidneys were retrieved: 70 from HBD and 26 from NHBD. Eleven from HBD and ten from NHBD were unsuitable for transplantation. At our institution, 68 kidney grafts were transplanted: 52 (76 per cent) were from HBD and 16 (24 per cent) were from NHBD. There was no initial function in 15 kidneys (29 per cent) from the HBD group, although 12 ultimately recovered. In the NHBD group, eight grafts (50 per cent) had initial non-function, two of which recovered. It is noteworthy that four of the grafts that failed in this latter group were obtained from only two donors. There were no significant differences between HBD and NHBD groups with respect to initial function. Forty-four of the 52 kidneys transplanted from HBD (85 per cent) and eight of the 16 grafts obtained from NHBD (50 per cent) have achieved good long-term function ($P = 0.01$). Mean serum creatinine values were 132.7, 115.0 and 115.0 $\mu\text{mol l}^{-1}$ at 1, 6 and 12 months, respectively, in the HBD group, and 292.0, 132.7 and 106.2 $\mu\text{mol l}^{-1}$ at the same time intervals after transplantation in the NHBD group.

We conclude that the use of NHBD significantly increases our institution's potential for kidney procurement, and that kidneys obtained from such donors can provide excellent function.

Late reperfusion of cadaveric kidneys does not reduce delayed primary function

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Reperfusion of cadaveric kidneys before transplantation has been claimed to reduce delayed primary function due to acute tubular necrosis¹. In this prospective randomized trial on cadaveric kidneys cooled and stored in hyperosmolar citrate (HOC), 35 kidneys were reperfused with 400 ml cold HOC before transplantation and 31 kidneys were not reperfused. All patients were managed according to well established treatment protocols. Other variables likely to influence the delayed function were equally distributed in both

groups, as shown in the Table. Delayed function was defined as need for dialysis in the first week after transplantation.

	Non-perfused (n = 31)	Perfused (n = 35)
HLA 1 or 0 mismatches*	8 (26)	10 (29)
HLA 2 or 3 mismatches*	23 (74)	25 (71)
Intraoperative blood pressure (mmHg)†		
Systolic	122(16)	119(33)
Diastolic	72(11)	75(13)
Second warm ischaemia (min)†	30.6(8)	34.0(10)
Cold storage time (h)†	26.4(7)	27.3(9)
Delayed function*	7 (23)	7 (20)

*Values in parentheses are percentages; †values are mean(s.d.). HLA, human leucocyte antigen

The results show that reperfusion does not reduce the incidence of acute tubular necrosis requiring dialysis as previously claimed.

1. Parrott NR, Forsythe JLR, Matthews JNS *et al.* Late perfusion. *Transplantation* 1990; **49**: 913–15.

Monitoring of kidney transplant patients with flow cytometry

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We followed up the circulating lymphocyte subpopulations in 36 transplanted patients in the early (30 days) postoperative period. Eleven were treated by prednisolone/azathioprine (PRED/AZA) and 25 by cyclosporin A (CyA)/PRED/AZA. During the first week after transplantation the number of PBMC, lymphocytes, CD3⁺, CD4⁺, CD8⁺ T cells decreased compared with results before transplantation. B lymphocytes slightly decreased during the 3 days, after which they reached the pretransplant level. The percentage positive lymphocytes and monocytes did not change significantly, but the antigenic expression markedly decreased.

During the fourth week after transplantation the recipients slowly recovered the pretransplant levels of PBMC and lymphocytes, without reaching those of healthy controls in either case. The T cells and their subsets, as well as B lymphocytes, reached the same levels as healthy controls at the end of the first month. The changes in the cell population were stronger, when expressed in patients with conventional immunosuppression, in comparison with those treated by CyA/PRED/AZA.

In conclusion, phenotypic flow cytometric analysis of circulating lymphocyte subsets can be useful for monitoring immunosuppression in patients undergoing kidney transplants to prevent complications.

Results of 118 cases of cadaveric renal transplantation

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In the Transplantation Unit of Istanbul Medical Faculty 118 cadaveric renal transplantations were performed between November 1987 and November 1991. The youngest donor was aged 7 months and the oldest was 64 years. The mean age was 17.4 years. There were 56 male and 20 female donors. The main cause of death was road traffic accident (41 cases) and the second most frequent cause was fall (26 cases). The most common blood group was A.

The youngest recipient was aged 11 years and the oldest 62 years. The mean age was 36.2 years. There were 66 male and 52 female recipients. The aetiology of the chronic renal failure of the recipients was chronic glomerulonephritis in 83 per cent of cases, chronic pyelonephritis in 16 per cent and renal amyloidosis in 1 per cent. Among the recipients the most common blood group was A (27 men, 24 women). Of the recipients, 113 had their first, four had their second and one had his third renal transplantation. At tissue typing 69 recipients were found to have three mismatches (MM), 48 had two MM and one had one MM.

The cold ischaemic time of the transplant kidneys ranged from 2 to 40 (mean 20) h. The warm ischaemic time varied between 0 and 2

min and the second warm ischaemic time was 36–45 min. A triple α -immunotherapy protocol was used, consisting of cyclosporin A, azathioprine and prednisolone in usual dosage. In one DR MM and in second or third transplantations therapy started with antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) (21 days), azathioprine and prednisolone. An attempt was made to treat acute rejection episodes with ATG or ALG (21 days) and, if successful, after 21 days the normal immunotherapy protocol was continued.

The most frequent complication was urinary tract infection (12 per cent, 14 cases) and the second frequent complication was pneumonia (11 per cent, 13 cases). The early mortality rate (0–1 month) was 9 per cent (11 cases) and the late mortality rate (1–30 months) was 13 per cent (15 cases). The survival rate of the recipients after 12 months was 85 per cent and the survival rate of the grafts after the same period of time was 78 per cent.

Effect of local therapy with transforming growth factor beta-2 on dog kidney allograft survival: a dose-response relationship

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The immunomodulatory potential of intrarenal transforming growth factor β_2 (TGF- β_2), a cytokine, was examined in ten canine renal allografts. TGF- β treatment in allogeneic and xenogeneic islet transplantation models resulted in reduced tissue immunogenicity and prolonged graft survival. The underlying mechanism is likely to be a profound inhibition of alloantigen presentation. Conventional local immunosuppressive therapy has been shown to effectively inhibit the cellular immune response in graft rejection. Regional drug application, moreover, offers the opportunity to reduce systemic side effects. Ten dogs were divided into pairs confirmed as histoincompatible by mixed lymphocyte culture. The left donor kidney was transplanted into the right iliac fossa of the recipient and a perfusion catheter implanted in the renal artery. Group I ($n = 4$) received no treatment; group II ($n = 2$) received pretreatment with 40 μ g TGF- β_2 ; group III ($n = 4$) received either 10, 20 or 40 μ g TGF- β_2 by catheter as a daily bolus for 10 days. Histological follow-up with biopsies was carried out at day 7 and autopsy. The end point of graft survival was determined by a creatinine increase of $>1000 \mu\text{mol l}^{-1}$. The histological grade of rejection was scored as 0 (slight and focal cell infiltration and slight parenchymal disturbance) to 4 (diffuse and marked cell infiltration with severe parenchymal disturbance).

Group	TGF- β_2 treatment (daily)	Histological grading of rejection (0–4)	Graft survival (days)
I ($n = 4$)	None	4	6,6,7,8
II ($n = 2$)	40 μ g pretreatment	4	8,8
III ($n = 4$)	10*, 20, 40† μ g	0	11*, 13, 16, 15†

Local TGF- β_2 therapy administered daily over a 10-day period showed a clear-cut and dose-dependent effect on dog kidney allograft survival; pretreatment was ineffective. This effect was confirmed histologically by a lesser degree of rejection in the treated animals. Systemic side effects were not detected. Moreover major histocompatibility complex class II expression in treated grafts and serum cytokine levels, such as interferon γ , were down-regulated.

TGF- β_2 , locally applied, seems to inhibit allograft rejection, for the duration of the treatment, the effect being most pronounced with the highest dose. Since TGF- β_2 is supposed to act by an inhibition of alloantigen presentation, one could speculate on a positive synergistic effect with cyclosporin A, which blocks effector mechanisms of rejection affecting predominantly interleukin 2 secretion by activated T lymphocytes.

Original modification of the cuff technique for orthotopic liver transplantation in the rat

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A modification of the cuffs used for portal vein and infrahepatic vena cava anastomoses according to Kamada's technique in orthotopic liver transplantation in the rat is proposed. Cuffs are produced from

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various calibre expanded polytetrafluoroethylene (PTFE) splints used for arteriovenous fistulae for dialysis. Three notches are made at 120° to each other in the middle of the cuff; the depth of the notches corresponds to the thickness of the splint. The procedure is then continued according to Kamada's technique. The notches allow the circumferential suture of the cuffs to the graft and the subsequent connection of the graft to the recipient vein; because the notches are restricted to the thickness of the splint, they do not produce luminal

changes, which may modify blood flow. We carried out 30 transplants in the rat using this technique and found circumferential suture easy to perform during preparation of the cuffs on the bench in solution at 4°C. The circumferential suture finds its place by itself without slipping out of the cuff while the knot is tied. Similarly, the difficult connection of the recipient vein to the graft is made easier. This small original modification, allowing a tighter connection of the veins to PTFE splints, makes the anastomoses on cuffs more secure.

Increased clearance of polymeric immunoglobulin A from the blood into traumatized tissues in rats

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Bacterial translocation may be enhanced by the 75 per cent decrease in biliary secretory immunoglobulin A (sIgA) content observed after thermal injury in the rat. We examined the hypothesis that this decrease relates in part to an altered clearance of polymeric IgA (pIgA) from the circulation.

Radiolabelled pIgA was injected into the femoral vein of rats 24 h after bile duct ligation. The rats then received a scald burn of 25 per cent of the dorsal body surface area, or sham treatment under ether anaesthesia. Total, trichloroacetic acid-precipitable, and immunoprecipitable radioactivity was assessed at intervals up to 24 h. To assess organ deposition of radioactivity after 1 and 24 h, two sets of animals were perfused with 120 ml saline, and radioactivity in skin, muscle and liver was measured.

In sham-treated and burn-injured animals, 68 per cent and 78 per cent, respectively, of the radioactivity was cleared from the circulation after 24 h, demonstrating a significant ($P < 0.003$) increase in clearance after burn injury. Radioactivity accumulated at the burn site during the 24 h after thermal injury. Radioactivity in burn-injured skin and in the latissimus dorsi of the burn-injured area was significantly increased compared with the equivalent areas of the sham-treated animals. Similar results were obtained 1 h after thermal injury.

Clearance of pIgA from the circulation is significantly increased after thermal injury. It appears that pIgA accumulates in the burn-injured site. Increased clearance of pIgA to sites other than liver may contribute to the decrease in biliary sIgA and to the compromised intestinal barrier observed after thermal injury.

Iatrogenic arterial trauma associated with hip fracture surgery

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Among all reported iatrogenic arterial injuries associated with hip joint surgery, 21 per cent can be related to correction of hip fractures. The paper presents three cases of iatrogenic arterial injury that occurred following hip fracture correction. The incidence of such lesions is estimated. During the period 1986–1990, 1417 patients with hip fracture were treated surgically in our hospital. At operation, three iatrogenic arterial injuries occurred (0.2 per cent). In two patients the profunda femoral artery and in one patient the common femoral artery were involved. The mechanisms of injury were: screw protrusion beyond the medial border of the femur in the first patient; arterial tear due to bone spiculae in the second; external pressure to the artery from an avulsed lesser trochanter in the third. The clinical findings were false aneurysm in two of the patients and distal ischaemia in the third. These three cases were managed surgically. In two, the defect of the artery was repaired with lateral sutures and in one a short interposition vein graft was used. Recovery was uneventful. Even in the best hands, arterial iatrogenic injuries can occur during hip fracture correction. The reported frequency of such events is extremely low. Early diagnosis of these lesions is of paramount importance.

Management of arterial injuries combined with fractures and dislocations of the leg

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Fractures and dislocations of the leg combined with arterial injuries lead to amputation in more than 50 per cent of cases. Twenty-two patients with such a lesion were treated at our clinic from 1986 to

1991. Because of a standardized preoperative clinical and ultrasonographic examination the arterial injury in all cases was documented. After a primary debridement all compartments were examined. The bones were stabilized by external fixation. The reconstruction of the artery, and in eight cases the veins, followed. Five patients needed a direct suture of the vessel and 15 a reversed saphenous vein bypass for reconstruction. Two patients with an injury of one of the three lower leg arteries did not need a reconstruction. Wounds were left open and dressed each day. When the wounds showed good granulation, a free muscle flap or meshgraft skin transplant finished the treatment. Using this preoperative and intraoperative protocol it was possible to decrease the amputation rate to 18 per cent. More than 80 per cent of these patients had good function of the leg with minor restriction.

Dysregulation of the human B cell system after trauma

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Immunoglobulin (Ig) synthesis is important in host defence against bacterial infection. Total Ig synthesis is increased after tetanus toxoid (TT) immunization. The object of the present study was to determine whether trauma alters spontaneous and mitogen-stimulated Ig synthesis *in vitro*.

Patients with blunt and sharp trauma injury (T), and healthy control subjects (C) were studied. All subjects were TT immunized on day 0. Blood mononuclear cells were harvested at intervals and cultured without (Unstim) or with pokeweed mitogen (PWM), a T cell-dependent B cell mitogen. After 10 days in culture, cumulative IgG and IgM levels in supernatants were measured.

Group	Day	n	Unstim	PWM	Difference
C	0–1	9	547(248)	2038(449)	1491(314)*
T	0–1	10	923(550)	2261(1104)	1338(1059)*
C	5–7	9	800(182)	2549(1036)	1749(943)*
T	5–7	11	2286(1043)	1839(722)	–447(335)*†
C	12–15	9	938(243)	2497(499)	1558(398)*
T	12–15	5	783(592)	2857(1300)	2074(1242)*

Values are mean(s.e.m.) concentrations in nanograms of IgG per culture well. * $P < 0.05$ (Unstim versus PWM, paired *t* test); † $P < 0.05$ (T versus C, same day, unpaired *t* test)

Spontaneous IgG synthesis was increased on days 5–7 among trauma patients, but not uniformly. PWM stimulation increased synthesis early (days 0–1) and late (days 12–15) after trauma, comparable to controls. Between 5 and 7 days after trauma, PWM reduced IgG synthesis rather than the normal increase. For IgM (data not shown), the same pattern was observed.

In conclusion, after trauma, B cells are not uniformly spontaneously activated. However, there is a period when PWM decreases, rather than increases, Ig secretion. This suggests a state of dysregulation of the human B cell system after injury.

Thromboxane A₂ as a mediator of skeletal muscle reperfusion injury

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Thromboxane A₂ (TxA₂) can cause vasoconstriction, platelet aggregation and neutrophil adhesion. The aetiological role of TxA₂ in skeletal muscle reperfusion injury was investigated in a rat model using the specific TxA₂ receptor antagonist GR32191. Thirty minutes before releasing a tourniquet applied to one hindlimb for 6 h, 12 rats had intravenous GR32191 ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$), ten control rats had no treatment and ten normal rats no ischaemia. Gastrocnemius muscle blood flow (GMBF, radiolabelled microspheres) at 10, 120 and 240 min reperfusion (matched times in normal rats) was measured

and a perfusion index (study:contralateral limb) calculated; percentage muscle viability was also quantified (GMV; histochemical staining plus planimetry). The Mann-Whitney *U* test was used to determine significance.

	Normal	Control	GR32191
GMBF			
10 min*	1.05 (0.68-1.18)	0.08 (0.01-0.13)	0.76 (0.29-1.31)
120 min*	0.97 (0.79-1.13)	0.29 (0.09-0.59)	0.82 (0.30-1.56)
240 min*	1.01 (0.73-1.16)	0.05 (0.01-0.14)	0.65 (0.26-0.89)
GMV	100 (100-100)	52.3 (33.2-61.4)	100 (70.1-100)

Values are median (interquartile range). * Minutes reperfusion

Controls *versus* normals demonstrated low reflow, low relative reperfusion and low reperfusion injury at 10, 120 and 240 min ($P < 0.01$; $P < 0.05$; $P < 0.01$) with muscle necrosis ($P < 0.01$). GR32191 enhanced GMBF throughout revascularization and also preserved muscle viability ($P < 0.01$ *versus* controls; P not significant *versus* normals).

This study implicates Tx_{A2} as an important mediator of skeletal muscle reperfusion injury and demonstrates an adjuvant role for its receptor antagonists in the surgical management of acute limb ischaemia.

Resorbable and bioactive implants of hydroxyapatite and poly(L-lactide): a mechanical and histological evaluation in goats

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In the development of new materials for resorbable systems for fracture fixation or bone replacement, composites of hydroxyapatite and poly(L-lactide) (HA-PLLA) were tested. These composites combine a biocompatible and bioactive ceramic (HA) with a biocompatible and resorbable polymer (PLLA).

In a transcortical implantation model in goats, six different plugs (5 × 7 mm) were inserted in the diaphyseal area of each femur: PLLA, grit-blasted PLLA (GPLLA), PLLA reinforced by incorporating 30 (C30) or 50 (C50) per cent weight HA, PLLA plasma-sprayed with a 50-µm HA coating (HAcP) and 316-L steel (S) as a control. At each follow-up period, after 3 and 6 weeks and 3 and 6 months, four animals were killed. In addition, two animals survived 1 year. Interfacial shear strengths, one of the parameters describing bone bonding, were evaluated in a push-out test of each left femur. This test records the force that is needed to push an implanted plug out of its cortical surrounding. Only plugs with comparable roughnesses can be compared because materials and not surface characteristics were the issue of this study. PLLA, C30 and C50 had comparable roughnesses (1-1.5 µm) as had GPLLA and HAcP (8-11 µm). In both groups statistical analysis of variance showed ($P < 0.01$) that C50 or HAcP had increased interfacial shear strength, after 3 months of implantation, when compared with the unfilled GPLLA. The control S showed no push-out strengths throughout all implantation periods. In support, histology of both right and left femur gave evidence, on a light microscopic level, of increased bone apposition at the interface for both composites and HA-coated PLLA compared with GPLLA. After 1 year of implantation no push-out strengths could be recorded. Histology showed a resorbing PLLA matrix turning the plugs into jelly-like materials.

In conclusion, mechanical and histological investigation of the bone-implant interface showed that these bioresorbable composites might be a welcome addition to implants used for fracture fixation or bone replacement in orthopaedic surgery.

Alcohol and injury severity: a review of road trauma

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Alcohol intoxication is a well recognized cause of road traffic accidents, but a relationship between the level of intoxication and injury severity has not been clearly established. To assess this

relationship, 820 consecutive road accident victims presenting to a large general hospital were studied retrospectively. Blood alcohol concentration results were obtained in 429 of the 535 eligible patients and were raised above the legal limit of 50 mg per 100 ml (0.05 per cent) in 57 cases (13 per cent). Injury severity, measured with the injury severity score (ISS), was compared with blood alcohol in three ways. The first way was by using Spearman's rank correlation on all 429 patients. The coefficient (ρ) of 0.27 indicated a highly significant correlation ($P < 0.01$). Second, the mean ISS of intoxicated patients (blood alcohol ≥ 0.05 per cent) was compared with that of sober patients and found to be significantly higher (Mann-Whitney *U* test, $P < 0.01$). Third, the distribution of intoxicated and sober patients across categories of injury severity corresponding to minor, moderate, severe and critical injury were compared using χ^2 analysis. This showed an increasing tendency for intoxication to be present as patients went from minor to critical injury ($P < 0.01$). Of the road user groups studied, pedestrians had the highest rate of intoxication and the highest mean blood alcohol levels. We conclude that there is a significant association between blood alcohol level and injury severity in road accident victims treated at a large general hospital.

Early management of the multiply injured patient

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The early management of multiply injured patients is important in optimizing the outcome. During 1990 and 1991, 137 patients with multiple trauma were studied. Of these, 39 died, 24 in the first 24 h, from cardiovascular arrest, hypovolaemic shock and intracranial injury.

The mortality rate improved from 32 per cent in 1990 to 24 per cent in 1991. We present an audit of our results and our analysis of therapeutic aims.

Prevention of acute renal failure by aggressive fluid resuscitation in patients with multiple injuries

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Acute renal failure still represents a serious complication in the early phase of the treatment of patients with multiple injuries. In 10-20 per cent of cases this leads to chronic haemodialysis or haemofiltration, so prevention is of utmost importance.

From 1982 to 1988, 472 patients were admitted to our clinic with multiple injuries, of whom 262 had suffered acute injury and were subjected to aggressive fluid resuscitation in the first few hours of admission. The regimen consisted of rapid infusion of 3000 ml Ringer's lactate with sodium bicarbonate until the patient was stabilized. The infusion was then adjusted to maintain a diuresis of 60-100 ml h⁻¹. Monitoring included pulse, blood pressure, central venous pressure, oxygenation, blood pH and diuresis. The haemoglobin and electrolytes were checked and corrected accordingly. Renal excretion was found to be the most sensitive parameter for successful fluid replacement.

Of the 262 patients thus treated, 112 were in shock on admission; 32 developed renal complications such as bacteruria, haematuria, impaired renal function and acute renal failure. Acute renal failure occurred only in the course of treatment in the intensive care unit and never during the first days.

Aggressive fluid resuscitation with large amounts of crystalline solutions is successful in the prevention of acute renal failure, which was rarely seen in severely injured patients after this form of treatment was introduced.

Intra-abdominal injury following blunt trauma

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In an attempt to determine objective criteria associated with severe injury, we performed a prospective study of patients admitted with blunt abdominal trauma.

The initial injury severity score (ISS) was established according to the scale devised by Mayer *et al.*¹. From January 1982 to June 1986 routine ultrasonography (US) of the abdomen was performed by a fully trained radiologist in all haemodynamically stable patients (group 1). From July 1986 to December 1990 computed tomography (CT) of the abdomen was used instead of US (group 2). The overall accuracy of these two diagnostic tests was assessed by recording the number of abdominal lesions of clinical significance found at operation and missed by the tests (false-negative test).

	Group 1 (n=73)	Group 2 (n=85)	P
ISS mean, median (range)	16, 12 (4-57)	19, 14 (3-75)	n.s.
No. undergoing operation*	13 (18)	11 (13)	n.s.
Total no. of deaths*	3 (4)	4 (5)	n.s.
No. of surgical deaths*	3 (23)	4 (36)	
No. of false-negative tests	4	4	n.s.
Spleen	0	0	
Liver	2	2	
Kidney	2	2	
Pancreas	0	0	

*Values in parentheses are percentages. n.s., Not significant

US and CT have identical diagnostic accuracy in detecting clinically significant injuries, provided US is performed by a dedicated senior physician. Whichever test is used it cannot reliably predict the outcome of the patient, or act as a substitute for serial assessments by a fully trained surgeon of the clinical and haemodynamic status of the patient.

1. Mayer T, Matlak ME, Johnson DG, Walker ML. The modified injury severity scale in pediatric multiple trauma patients. *J Pediatr Surg* 1980; **15**: 719-26.

Traumatic intrapericardial diaphragmatic hernia

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The purpose of the present study is to report a case of traumatic intrapericardial diaphragmatic hernia and to review the literature.

A 61-year-old woman sustained a blunt injury with rib fracture, head injury and pelvic fracture in a traffic accident. She developed a left pleural effusion that was drained. The patient was transferred to the trauma ward and 20 days later she was discharged home. One month later she presented with thoracic pain and dyspepsia. Chest radiography revealed air within the outline of the heart. A barium meal and enema revealed herniation of the stomach and colon into the chest cavity. Laparotomy was performed. A defect was found in the central tendon; transverse colon, stomach and greater omentum had herniated into the pericardium. These viscera were reduced and the defect repaired with a synthetic graft. The postoperative course was uneventful.

Sixty-three cases of traumatic intrapericardial diaphragmatic hernia have been reported; the majority of patients presented after traffic accidents. Because of associated injuries, diagnosis is generally delayed. Symptoms most frequently encountered were abdominal pain and dyspnoea. Barium contrast studies and computed tomography (CT) proved to be the most useful; however, barium studies are not without risk (the procedure may precipitate cardiac tamponade) and are contraindicated in patients with signs of intestinal obstruction. The organs most frequently herniated were the transverse colon, stomach and greater omentum. In delayed presentation, thoracotomy has been preferred; however, laparotomy is preferable. Previously, most authors have used interrupted non-absorbable sutures, but now polyglactin is preferred.

We conclude that the most accurate diagnostic studies are barium studies and CT. Barium studies are contraindicated in patients with signs of intestinal obstruction. The transabdominal approach is preferred in traumatic and delayed presentations. Polyglactin is the suture material of choice.

Computed tomographic detection of septic focus after severe blunt chest trauma

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Well known problems in the treatment of severe blunt chest trauma are lung contusion with long-term respiratory therapy and pulmonary septic complications with no obvious focus detectable by conventional radiography. From July 1988 to October 1991 we treated 87 patients with lung contusion: 21 patients became septic and 12 developed severe sepsis with adult respiratory distress syndrome or multiple organ failure.

Because we could not detect a septic focus by conventional radiography, all 21 patients underwent thoracic computed tomography (CT). Three patients underwent thoracic CT twice; 11 had gangrene of the lower lobe, ten had empyemas and three had massive infiltration with areas of pneumonia.

Gangrene was treated by six resections of the lower lobe and three minithoracotomies with drainage; empyema was treated by seven thoracotomies and drainage and in three cases by drainage alone. The fever decreased within a few days after surgery and all patients were discharged from intensive care.

The indications for thoracic CT after blunt chest trauma, lung contusion and septic complications must be set generously to include deterioration of respiratory parameters without changes detectable by radiography or without detection of a septic focus, persisting septic conditions and suppurating bronchoscopic aspirate.

Patients treated for trauma at a surgical department in the years 1950-1986

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Alterations in the number of patients treated for trauma reflect both the development of motorized transport and changes in the population.

Analysis was performed based on 2-year periods at 5-year intervals. There was a constant increase in the number of patients, which in 1985-1986 was 2.5 times that treated in 1950-1951. Injuries of the head and musculoskeletal system were the most common throughout the period analysed, and in the last 2 years they comprised over 60 per cent (823) of inpatients. There was also a significant increase in the number of patients with multiple injuries. The inpatient population of 1985-1986 differed markedly from that of 35 years before. In the years 1950-1951 the percentage of patients aged over 60 years was 13.1 per cent (64), while 35 years later it was 28.7 per cent (376). However, mortality dropped from 7.9 per cent (39) to 4.2 per cent (55) over this period. A decrease in mortality was observed in all age groups, being most remarkable in patients aged 15-59 years.

It was concluded that the absolute number of patients treated for both injuries and multiple injuries has increased and that, despite an alteration in the age of the population of patients, a decrease in mortality was observed.

Abdominal trauma: surgical treatment

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The purpose of the present study was to assess the surgical treatment of patients with abdominal trauma managed at our institution.

From 1 January 1985 to 1 January 1991, 1105 patients with trauma were assessed. A total of 199 (18 per cent) had operations, and 120 (11 per cent) underwent operation because of abdominal trauma. The average age of the 120 patients was 33 (range 3-86) years, and 86 (72 per cent) were men.

The mechanism of injury was usually motor vehicle accident (87 cases; 72 per cent) and stab wounds (14 cases; 12 per cent). One hundred injuries resulted from blunt impact trauma, whereas 20 sustained penetrating trauma. The majority of victims had associated injuries (thoracic, 47; neurological, 44).

In addition to clinical assessment, diagnosis was made using plain

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radiography, ultrasonography and peritoneal lavage, the latter being most sensitive (97 per cent).

In all cases a median laparotomy was made. Solid viscus injuries were most frequent (44 liver injuries and 38 splenic injuries). The small bowel was injured in ten cases and the large bowel in eight. There were 28 retroperitoneal haematomas associated with other injuries. Generally the trauma was multiple, with 200 injuries in 120 patients.

The commonest procedures were splenectomy (32), liver suture

(32) and hollow viscus suture (18). Commonest complications were pulmonary, ten (8 per cent). Five patients were reoperated on, two for removal of gauze packing. Overall mortality rate was 11 per cent (13 patients).

We conclude that motor vehicle accident is the commonest cause of injury. The majority of victims of abdominal trauma have other associated injuries. Ultrasonography and peritoneal lavage are useful, with high sensitivity. Abdominal trauma carries a high mortality rate.

Ureteric distension and the reduced renal blood flow of obstructive uropathy

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This study was designed to investigate the role of ureteric distension in the reduction of renal blood flow that is known to occur in obstructive uropathy.

In an ovine model, a 5 Fr (10 × 0.5 cm balloon) angioplasty catheter was inserted retrogradely into the left ureter. To eliminate the other components observed in obstruction, a biluminal nephrostomy catheter was inserted into the left kidney to allow free drainage of urine. Right carotid and left femoral arterial lines were established to measure renal cortical blood flow by the radionucleotide microsphere method. After a 4-day recovery period, 1 × 10⁶ ⁵⁷Co-radiolabelled 15-µm microspheres were injected into the left ventricle with a reference sample being withdrawn from the femoral artery. Five study animals had ureteric balloon inflation and in five controls the balloon remained non-inflated. After 24 h a second blood flow measurement using ⁸⁵Sr-radiolabelled microspheres was performed. A Whitaker test, perfused at 11 ml min⁻¹, confirmed a non-obstructed left urinary tract. After kidney removal the cortex was dissected into outer and inner portions, weighed and counted along with the reference blood samples for radioactivity on a Packard Cobra QC 5003 γ counter. Renal blood flow was calculated by the standard microsphere method.

	Control (n=5)			Distension (n=5)		
	R	L	L%/T	R	L	L%/T
F1	278(64)	259(62)	48.2(1.6)	267(46)	254 (57)	48.5(5.6)
F2	273(71)	247(64)	47.5(1.6)	260(58)	252(48)	49.3 (4.6)
Change			-0.7(1.0)			+0.8(1.9)

Values are mean(s.d.). F1, first blood flow; F2, second blood flow; R and L, right and left cortex of kidney; L%/T, left kidney cortex percentage of total blood flow

The difference in the change between distended and control groups was 1.5 per cent, which is not significant. Moreover, 95 per cent confidence limits for the true differences were narrow (- 1 to + 3.9 per cent).

In conclusion, acute ureteric distension does not contribute to the known reduced renal blood flow of obstructive uropathy.

Canine urinary neosphincter formation using electrically stimulated striated muscle: preliminary results

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The superior belly of sartorius muscle was transposed into the abdominal cavity of four female dogs and activated by a pacemaker. Continuous low-frequency stimulation was used for 6 weeks to transform the skeletal type 2 muscle to a fatigue-resistant type 1 muscle. The urethral pressure was measured (mean 27 cmH₂O) and the prepared muscle was passed around the urethra and sutured to form a neosphincter. Urethral closure pressure profiles were performed before and during electrical stimulation of the neosphincter. The mean urethral closure pressure increased to 37.5 cmH₂O with non-stimulated neosphincter and 42 cmH₂O with electrically stimulated neosphincter. The mean urethral functional length was 55 mm before the creation of the neosphincter, 77 mm after creation of an unstimulated neosphincter, and 100 mm during electrical stimulation of the neosphincter.

Formation of a urinary neosphincter using electrically stimulated striated muscle can increase the urethral closure pressure and the urethral functional length. We intend to develop this canine model into a technique suitable for clinical application in urinary incontinence.

Three-dimensional visualization of velocity profiles in the abdominal aorta in unanaesthetized human volunteers

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To study the relationship between local haemodynamics and atherogenesis in the abdominal aorta, velocity profiles measured in the abdominal aorta of young, unanaesthetized volunteers were visualized three-dimensionally.

Vingmed CFM 750 colour Doppler equipment was used to measure point blood velocities in the abdominal aorta by applying the Doppler probe on the abdomen. The velocity information from every pixel in the colour flow image was downloaded directly from memory into a Macintosh computer with dedicated software.

Duplex two-dimensional colour flow mode was used for visualizing the flow fields qualitatively and for showing the angle of insomance. A multigate facility (colour M-mode) gave accurate velocity information along an anterior-posterior diameter. The velocity data were analysed off-line, where angle correction and three-dimensional visualization of the diameter velocity profiles were performed.

The velocity profiles had a characteristic triphasic appearance, with antegrade velocities during systole, retrograde velocities during early diastole, and then antegrade velocities again. The velocity profiles were skewed with highest velocities at the anterior vessel wall, retrograde velocities being most pronounced at the posterior vessel wall.

These findings are in accordance with previous *in vitro* studies, and show that velocity profiles in the abdominal aorta in normal unanaesthetized volunteers at rest are skewed, with changes in velocity direction during the cardiac cycle.

Community-based aortic aneurysm screening

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As part of a community aneurysm screening programme, 3500 men aged 65–75 years, from 20 urban general practices (77 GPs), received a single invitation to attend ultrasonographic screening for abdominal aortic aneurysm. Screening was carried out by a trained physicist at GPs' surgeries, using a Pie Data 150S portable ultrasonographic scanner with 3.5-MHz sector transducer. Maximal aortic diameter was measured in transverse and longitudinal planes. Ultrasonographic accuracy was established by comparison with computed tomography in 24 patients. (Standard deviation of differences between methods was 1.78 mm; standard error of the distribution of differences was 0.37 mm.)

In all, 2669 men (76 per cent) attended screening. Compliance varied between catchment areas (ranging from 52 per cent for inner city areas to 86 per cent for suburbs). Aortic imaging was successful in 97.3 per cent of scans.

Aortic diameters > 29 mm in diameter occurred in 219 (8.2 per cent) of screened patients. Of the patients with aortic diameters > 40 mm, 79 (3 per cent) have been referred for surgical assessment; 48 have undergone aneurysm repair. A group of 140 patients with aortic diameters of 29–40 mm are undergoing follow-up by serial 3-monthly ultrasonography to monitor aneurysm growth. Ischaemic heart disease was present in 21.9 per cent of patients with aneurysms ($P < 0.01$, χ^2 test); 18.3 per cent ($P < 0.01$) had previous myocardial infarcts with electrocardiogram or enzyme changes. Other peripheral vascular disease occurred in 13 per cent ($P < 0.01$); however, association of aneurysm formation with hypertension (19 per cent) and diabetes (5 per cent) was not statistically significant compared with the screened population.

Community-based ultrasonographic screening should contribute to reduced mortality rates from ruptured aortic aneurysm. It is an inexpensive, effective method of aneurysm diagnosis with high compliance from the at-risk cohort of an urban population.

Screening for familial aortic aneurysm

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There may be a familial basis for the development of abdominal aortic aneurysm (AAA). If so, first-degree relatives of patients with AAA could form an appropriate population for aneurysm screening. The aim of this study was to establish the prevalence of aortic enlargement in such a population.

Of 100 consecutive patients who had undergone AAA repair it was possible to contact the patient or their families in 94 cases. One hundred and ten first-degree relatives over the age of 50 years were identified. Seventy-six (38 men and 38 women; age range 50–87 years) have been screened with ultrasonography. Aortas were categorized as normal, dilated or aneurysmal with maximum anteroposterior diameters of <2.5 cm, 2.5–3.9 cm and >3.9 cm, respectively.

No aneurysms have been detected on screening. However, one brother and one sister were known to have had aneurysms previously. Dilated aortas were found in four of 23 brothers, four of 15 sons, one of 28 sisters and none of ten daughters. A total of nine of 39 male relatives (23 per cent) and two of 39 female relatives (5 per cent) had a dilated or aneurysmal aorta. Aortic enlargement is more common in male than in female first-degree relatives ($\chi^2 = 3.84$, $P = 0.05$), in approximately the same ratio as for the normal population, the prevalence in both groups appearing to be two to three times greater than the norms for age (P not significant).

These results support screening of male first-degree relatives. The value of screening of female first-degree relatives is unproven.

Ultrasonographic screening for abdominal aortic aneurysms in patients with peripheral vascular disease

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Abdominal aortic aneurysm (AAA) is an important cause of preventable death in the elderly. The mortality rate from ruptured aneurysm remains high, exceeding 50 per cent if you include prehospital and hospital deaths. The risk of death from elective aneurysm resection continues to decrease and is now in the range of 3–5 per cent. However, many AAAs are asymptomatic and the only way to diagnose these aneurysms before rupture is by screening. Ultrasonography is extremely accurate for detection of AAA and in the determination of aneurysm size. Therefore we decided to undertake a screening programme of a possible high-risk group of patients with coronary artery disease and/or peripheral atherosclerotic vascular disease.

We performed an abdominal aortic ultrasonographic examination in 110 consecutive patients aged 55–74 years (84 men and 26 women) who were referred to our cardiovascular surgical department because of suspected atherosclerotic extracranial arterial disease and/or coronary artery disease. On admission, all patients underwent a physical examination and Doppler pressure studies. The ultrasonographic criteria for aneurysm were defined as an infrarenal aortic diameter ≥ 3.0 cm or an infrarenal:suprarenal aortic diameter ratio of ≥ 2.0 . An incipient aneurysm was defined as a focal dilatation of the infrarenal aorta which was <3.0 cm in greatest dimension. In this group, the infrarenal:suprarenal aortic diameter ratio ranged from 1.1 to 1.9.

On physical examination, we detected one aneurysm. However, ultrasonography identified eight aneurysms (7.3 per cent) and seven incipient aneurysms (6.4 per cent). The diameter of the detected asymptomatic aneurysms ranged from 31 to 55 mm (one woman and seven men). The mean (s.d.) age was 64.3 (4.6) (range 60–74) years. No isolated iliac artery aneurysm was detected.

One of eight aneurysms was suspected clinically. The infrarenal:suprarenal diameter ratio ranged from 1.6 to 1.7. Iliac vessel diameter ranged from 8 to 15 mm. In seven incipient aneurysms, diameter was 19–26 mm, infrarenal:suprarenal diameter ratio ranged from 1.2 to 1.9 and iliac vessel diameter ranged from 9 to 14 mm.

We detected a high incidence of AAA in patients who were referred to our department because of peripheral vascular disease.

Within this group, the incidence of aneurysm was found to be 7.3 per cent, which is at least twice the estimated incidence in the general population. Our data suggest that, in patients with peripheral vascular disease, screening of the abdominal aorta by ultrasonography will detect a high incidence of asymptomatic AAAs.

Inflammatory aneurysms of the abdominal aorta

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In order to evaluate the incidence and clinical pathology of inflammatory aneurysms (IAs), we have reviewed 72 consecutive patients undergoing repair for abdominal aortic aneurysm in the past 5 years. Twenty-eight patients were selected because of accurate pathological study of the aneurysm; five (18 per cent) were operated on for IA, and 23 (82 per cent) for atherosclerotic aneurysm (AA). Preoperative diagnosis of IA was possible in one case (clinical, laboratory findings and computed tomographic scan). Clinical and pathological findings were statistically compared (IA versus AA) using χ^2 or Student's *t* tests. Mean (s.d.) age (71.4(7.8) versus 65.2(6.2) years), M:F ratio (4:1 versus 22:1), hypertension (40 versus 48 per cent), diabetes (0 versus 26 per cent), cardiac disease (40 versus 26 per cent), associated obstructive disease (20 versus 26 per cent) and symptoms (pain, 100 versus 87 per cent) were not significantly different. Histological evaluation gave the results shown in the Table.

	Pathological findings		P
	IA	AA	
Intima			
Heavy calcification	0	35	0.002
Adventitia			
Fibrosis	80	0	0.0001
Lymph dilatation	80	17.3	0.007
Lymphadenitis	100	4.0	0.0001
Inflammation	66.6	42	n.s.

Values are percentages. n.s., Not significant

We conclude that preoperative diagnosis of IA is difficult. Computed tomographic scans may identify severe IAs. No significant differences were shown from a clinical evaluation of IAs versus AAs.

Inflammatory aortic aneurysm

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Inflammatory aortic aneurysms (IAA) differ from ordinary aortic aneurysms in their clinical presentation and therapeutic approach. In this retrospective study, 108 cases of abdominal aortic aneurysms undergoing operation in the period 1977–1990 were evaluated and seven cases (6 per cent) of inflammatory aortic aneurysms were detected.

The mean age of the group with non-inflamed aortic aneurysms was 67 years, compared with 65.2 years for IAA. Six patients presented with sudden onset of abdominal pain radiating to the lumbar region; one patient was asymptomatic. Four patients also suffered weight loss. The sedimentation rate was moderately elevated in four patients and was normal in three. No abnormality in other laboratory tests or renal function tests occurred. Periaortic thickening of retroperitoneal tissues and thinning of the posterior aortic wall was demonstrated in four patients, and complete loss of the posterior wall was suspected by computed tomographic scanning in one patient: these cases were considered as preoperative IAA. All patients underwent operation. No mortality occurred during the early postoperative period (30 days). It was shown that graft interposition could be achieved safely by approaching the inlay through the aneurysm, thus avoiding extensive dissection.

In conclusion, IAA can be diagnosed before operation by recently developed non-invasive modalities, and repair may be performed with low morbidity and mortality by using a suitable surgical approach.

Inflammatory abdominal aortic aneurysms

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Over a 5-year period the diagnosis of inflammatory abdominal aortic aneurysm was made in seven of 85 cases of abdominal aortic aneurysm.

All patients were men and presented with abdominal and/or lumbar pain. In six cases the diagnosis was made by computed tomography (CT) scan or ultrasonography. One patient presented with concomitant unilateral hydronephrosis and one patient had simultaneous aortic type B dissection and a primary aortoduodenal fistula.

Five patients were treated by aneurysmectomy and graft interposition. Two were treated conservatively. One died 4 days later of rupture of the aneurysm. One patient died 14 months later from intercurrent disease. No associated infectious or collagen disease was detected in all seven patients. Pathological analysis of the aneurysm wall in five patients revealed chronic inflammatory changes consisting of plasma cell and lymphocytic infiltrates with increased hyaline collagen deposition in the adventitia. Microbiological cultures from the contents of the aneurysms were negative.

Based on a review of the literature and our own findings, we conclude that inflammatory abdominal aortic aneurysms are an unusual manifestation of atherosclerotic disease. Primary treatment consists of aneurysmectomy and graft interposition. In cases of hydronephrosis because of ureteric obstruction owing to perianeurysmal fibrosis, ureterolysis in combination with aneurysmectomy and graft interposition is recommended.

If aneurysmectomy is technically not feasible, an extra-anatomical bypass procedure is to be considered. Conservative treatment is only considered when there is an absolute contraindication to operation. Corticosteroid therapy is then initiated with frequent CT scans to evaluate the progress of therapy.

Transperitoneal versus extraperitoneal approach for routine vascular reconstruction of the abdominal aorta

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Although most authors prefer the extended posterolateral retroperitoneal approach to the abdominal aorta, in some circumstances, such as suprarenal aneurysmal disease, only a minority of surgeons believe that this should be the technique of choice for uncomplicated abdominal aortic reconstruction.

In this non-randomized retrospective study, 169 elective reconstructions of the infrarenal aorta were included (January 1990 to April 1991). The surgical approach was transperitoneal (TP) in 79 cases (47 per cent) (midline 72, transverse seven) and extraperitoneal (EP) in 90 (left side 88, right side two). Each phase of the EP operation took longer than for the TP approach. The times from induction to incision, from incision to aorta cross-clamp, and from incision to the end of the procedure were longer in the EP group, respectively 61 versus 44 min ($P = 0.0001$), 55 versus 46 min ($P = 0.015$) and 193 versus 173 min ($P = 0.027$). In the EP group more units of blood were transfused (2.8 versus 2.3 units, $P = 0.0154$) and a higher amount of colloid was administered (2.1 versus 1.8 litres, $P = 0.031$). However, the nasogastric tube could be removed earlier in the postoperative period in the EP group (2.5 versus 4.4 days, $P = 0.0019$). The mortality rate was 2.2 per cent (two of 90) in the EP and 1.3 per cent (one of 79) in the TP group. In total, 26 patients in the EP group had at least one complication (29 per cent) versus 19 patients in the TP group (24 per cent). Most complications were evenly distributed between the groups. In the TP group, however, five patients (6 per cent) had a prolonged period of ileus, while this complication did not occur in the EP group ($P = 0.015$).

It is concluded that in spite of a higher proportion of risk factors, a longer preparation, dissection and total procedure time, the need for more blood transfusion and colloid in the EP group, the incidence of complications is not higher compared with the TP group. Problems of intestinal transit were found exclusively in the TP group. Therefore this study adds to the findings of other retrospective studies that the EP approach is better tolerated by patients and might be the technique of choice for simple elective infrarenal aorta reconstructions.

Abdominal aortic aneurysm rupture: factors affecting outcome of surgical treatment

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Rupture represents a catastrophic life-threatening complication of abdominal aortic aneurysm (AAA). A review of 59 consecutive patients with ruptured AAA, admitted to our teaching hospital from 1 January 1986 to 31 January 1990, has been carried out to determine the cause of death. Ruptured aneurysms were repaired in 53 patients, with intraoperative and overall 30-day mortality rates of 9 per cent (five of 53) and 36 per cent (19 of 53) respectively. Six patients died either before surgery or where surgery was considered inappropriate because of age (over 85 years), hypotension (systolic blood pressure <80 mmHg) or history of coronary heart disease.

The parameters influencing survival were systolic blood pressure <100 mmHg on admission, increasing age, chronic obstructive airway disease, history of more than one myocardial infarction and operative blood loss. The observed differences were not statistically significant. The demonstration of a risk index for patients with ruptured AAA was not possible. With this life-threatening condition we suggest that outcome is measured in terms of survival rather than morbidity. Education of the surgical team and emergency room physicians might expedite the diagnosis of ruptured AAA with a subsequent improvement in outcome.

Banding of aortoiliac aneurysms in patients at high risk

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The purpose of this study was to examine whether external reinforcement or banding of non-ruptured abdominal aortoiliac aneurysms, as advocated by Robicsek in the early 1970s, is a feasible alternative to conventional prosthetic replacement in selected high-risk patients. Therefore, in a prospective study all high-risk patients with an ASA score of III or more (American Society of Anesthesiologists) and/or aged over 70 years and presenting with aneurysmal disease were selected. Patients with non-ruptured aneurysms of the abdominal aorta and/or iliac arteries, at least 6 and 4 cm in diameter, respectively, were included.

In an elective procedure the aneurysm was carefully mobilized circumferentially through a midline laparotomy incision and a longitudinally opened Dacron (DuPont) prosthesis was fitted around the aneurysm, just tight enough to contain the pulsatile wall expansion. When necessary this on-site tailored design was modified with a segment above the renal arteries. Care was taken to secure correct maintenance of banding position. No aortic cross-clamping was used and no anastomosis had to be performed. All procedures were finished within a 2-h time limit. There was no substantial blood loss; transfusion of blood components was not required.

Six aneurysms in five patients (mean age 74.4 years; male:female ratio 4:1) have been operated on from 1988 to the present, applying this technique to five aortic and one iliac aneurysm. One patient died 9 months after operation from severe bronchopneumonia unrelated to the procedure; the others are still alive. Patients are seen on a 3-monthly basis during the first year for ultrasonography. Later, they visit every 6 months and receive routine intravenous aortography once a year (mean follow-up 24.4 months, Kaplan-Meier statistic). No distal embolism has been observed and all patients are symptom-free at the present time. We therefore conclude that in selected high-risk patients presenting with a non-ruptured abdominal aneurysm, banding can provide a valuable, safe and minimal procedure to prevent rupture.

Thrombolysis-angioplasty of failed arterial grafts

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This study examined the long-term clinical success and complications of thrombolysis-angioplasty (TLA) of failed arterial grafts performed in 17 patients (group 1) and matched with 21 patients (group 2) who had thrombolysis followed by graft revision. TLA consists of alternating thrombolysis and percutaneous transluminal angioplasty (PTA) in the treatment of occlusive arterial disease.

The study group consisted of 21 autologous vein grafts, six ovine collagen grafts, six polytetrafluorethylene prostheses, three human umbilical vein and two polyurethane vascular grafts. All bypasses were below the knee; 13 were to the tibial level. Thrombolytic agents used were urokinase in 21, tissue plasminogen activator in 13 and streptokinase in four cases. Following successful thrombolysis, PTA was performed with a 3-5-mm balloon catheter. Ten distal anastomotic stenoses, two graft strictures and five peripheral stenotic lesions were the main factors causing graft occlusion.

The initial success rate in group 1 was 71 per cent (12 of 17 grafts). Life-table analysis of clinical success rate was 36 per cent at 1 year and 21 per cent at 2 years. In all, ten grafts failed at follow-up; in six of these cases secondary intervention was unsuccessful. Failures occurred in eight of ten anastomotic stenoses, in one of five with run-off lesions and in one of two vein graft strictures. Limb salvage rate was 82 per cent at 1 month and 60 per cent at 48 months. In group 2, clinical success rate was 60 per cent at 1 year and 47 per cent at 2 years. Because of the small number, statistical significance was not achieved ($\chi^2 = 1.91$).

The results suggest that thrombolysis of failed distal grafts has poor long-term clinical success. Results of balloon angioplasty are inferior to those of graft revision. Emphasis should be placed on early detection and repeat autologous vein graft bypass.

Primary amputation or vascular reconstruction in the elderly with critical limb ischaemia

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Fifty-one immobile housebound patients over the age of 75 years who underwent reconstructive vascular surgery for critical limb ischaemia were compared with 33 patients who underwent primary amputation. The average age at operation of those undergoing reconstruction was 79.8 years, and those having amputation 82.1 years.

There were no significant differences in the prevalence of risk factors in the two groups; although 75 per cent of those having reconstruction were smokers, compared with 58 per cent of amputees, and only 25 per cent of patients reconstructed were diabetic compared with 50 per cent of those having amputation. The prevalence in the reconstruction and amputation groups of ischaemic heart disease was 35 per cent and 41 per cent, hypertension 28 per cent and 25 per cent, and of risk likely to limit life expectancy 55 per cent and 50 per cent, likely to limit mobility 53 per cent and 47 per cent and likely to affect anaesthesia 35 per cent and 30 per cent respectively.

The perioperative mortality rate was higher after amputation (30 per cent) than after reconstruction (6 per cent). Hospital stay was also longer after amputation (mean 41.6 days) compared with reconstruction (mean 33.4 days). Some 84 per cent of patients returned to their own home after reconstruction compared with only one-third of patients after amputation. Mobility outside the home was achieved in 43 per cent who had reconstruction but only 3 per cent of amputees. The 3-year survival rate was also greater after reconstruction (72 per cent) than after amputation (28 per cent).

These groups were not randomized but they are broadly similar in the presence of preoperative risk factors. Vascular reconstruction provides superior results in mobility, early and late mortality, independence of life and cost to health services. This justifies an aggressive policy of reconstruction in the elderly and suggests that such patients should be referred to a vascular specialist before primary amputation becomes inevitable.

Arteriovenous fistula in the management of the critically ischaemic lower limb

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Chronic lower limb ischaemia is most often secondary to arteriosclerosis; less common are small vessel diseases such as thromboangiitis obliterans. Lower limb ischaemia is a common disorder associated with a high risk of disability and premature death. Surgery has for many years been successful in the treatment of large vessel disease, but has only recently been applied to disease of the small vessels.

In 1990 and 1991, 20 patients were treated with venous arterialization. All patients were assigned to four groups according to Dardik criteria of distal flow, and were also grouped according to degree of clinical ischaemia (four groups). Venous arterialization was used in patients with severe ischaemia and poor peripheral flow (third and fourth groups).

Operations performed were saphenous vein arterialization alone (ten), with adjunctive popliteal arteriovenous fistula (four), or with distal arteriovenous fistula (six; five tibial and one peroneal).

One patient died on the third day. Of the survivors, eight required an above-knee amputation, while in four patients a more distal amputation was possible. Seven patients' limbs were saved.

In conclusion, the results of this series and data from other authors indicate that revascularization of the critically ischaemic limb should be attempted if possible.

Rapid anastomoses of small arteries using microvascular staplers

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The original microvascular staplers, with suction fixation of anastomosed arteries (diameter ≤ 2 mm), were used for end-to-end anastomoses in internal thoracic and occluded coronary arteries. Good postoperative results have been achieved in over 300 consecutive patients with 90 per cent patency rate in follow-up periods to 23 years. The procedure can be performed effectively on an arrested or beating heart with mean anastomosing time of 1–4 min.

An anastomosis in a still operation field, on arteries or tubular organs (extremities, transplantation, gynaecology, etc.), is easier and has potential for future technological advances. Microvascular staplers could effectively reduce surgical workload in difficult small vessel anastomoses.

Surgical treatment of acute lower extremity ischaemia in patients with atherosclerotic occlusive disease

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We report our experience of the management of acute lower extremity ischaemia in 76 patients with atherosclerotic occlusive disease in the last 5 years. Vascular reconstruction had previously been carried out on 18 patients. Patient selection, technical considerations and postoperative management will be described. The follow-up shows an improvement of patency rates in cases of reconstructive vascular surgery compared with patients who had thrombembolectomy alone.

Pharmacological reduction of the systemic effects of intermittent claudication

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The majority of patients with intermittent claudication are treated by exercise. Localized muscle ischaemia induced by exercise causes systemic vascular endothelial injury, resulting in increased permeability which is manifested as a measurable increase in urinary albumin excretion. Repetitive systemic vascular endothelial injury leads to accelerated atherogenesis and may explain the high mortality rate of claudicants. If exercise is to remain the mainstay of therapy then prevention of the systemic effects of repeated muscle ischaemia may be of benefit.

A xanthine derivative, oxpentifylline, prevents systemic vascular endothelial injury in animal models. A double-blind placebo-controlled crossover trial was undertaken to determine its effects on exercise-induced systemic vascular endothelial injury in 20 claudicants. Albumin excretion relative to creatinine (ACR) was measured before and after standardized exercise and after 1 week of treatment with either placebo or active drugs. The difference of ACR 1 h after exercise compared with before exercise was significant ($z = -2.2$, $P < 0.03$, Wilcoxon two sample test).

These results suggest that deleterious systemic effects of localized ischaemia can be attenuated pharmacologically in patients.

Prostacyclin adjuvant therapy during femorodistal reconstruction

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Infrainguinal arterial bypass graft patency is determined by blood flow, peripheral resistance and surface thrombogenicity. Iloprost, a stable prostacyclin analogue, is a potent vasodilator with platelet and neutrophil antiaggregatory properties. It reduces reperfusion injury after prolonged ischaemia, improves patency after topical application to small arterial anastomoses, and has been shown to improve femorodistal graft blood flow in the early postoperative period.

The effect of iloprost on peripheral resistance and graft blood flow during femorodistal bypass was investigated. Fifteen patients undergoing femorocrural saphenous vein bypass for critical ischaemia received 3 µg iloprost, infused into the graft via an unligated side branch over 2 min. Controls received placebo. Graft blood flow and peripheral resistance were measured using an operative Doppler flow meter. After operation, graft blood flow was measured by daily duplex ultrasonography for 7 days.

Iloprost produced an immediate drop in peripheral resistance in all cases from a median value of 0.91 (range 0.28–1.73) units to 0.49 (range 0.27–1.31) units ($P < 0.01$, Wilcoxon test), persisting to 20 min. Largest decreases in peripheral resistance occurred in patients with highest initial resistances ($r = 0.73$, $P < 0.01$). Median blood flow during the same period increased by 53 per cent from 99 to 151 ml min⁻¹ ($P < 0.01$) and was maintained over 7 days.

Iloprost should reduce the incidence of early femorodistal graft failure, particularly in those patients with low graft blood flow due to high peripheral resistances on completion of the anastomosis.

Evaluation of epidural spinal cord electrical stimulation versus conservative treatment in patients with critical ischaemia of the legs

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Management of patients with severe ischaemia of the leg in whom vascular reconstructive surgery is impossible or unsuccessful is restricted to conservative measures consisting of analgesic and vasoactive medication and local wound care. This often ends with amputation of the affected leg. Epidural spinal cord electrical stimulation (ESES), an accepted treatment for chronic pain, may help to relieve ischaemic pain and to heal ischaemic skin lesions.

In a pilot study, 37 patients with critical leg ischaemia were randomized, 19 to ESES (group 1) and 18 to conservative therapy (group 2). Inclusion criteria were: persisting rest pain and/or ischaemic skin lesions with a maximum diameter of 3 cm, Doppler ankle pressure < 50 mmHg or toe pressure < 30 mmHg, and informed consent. The cumulative 'lower extremity survival' rate after follow-up of 1 year was 65 per cent in group 1 and 31 per cent in group 2. In group 2, amputations ($n = 11$) tended to occur at an earlier point, a large number within 3 months. In group 1, amputations ($n = 6$) were performed between 2 and 6 months. Three patients died, one in group 1 and two in group 2.

Duplex assessment of clinically diagnosed venous insufficiency

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In a prospective study of 142 patients (104 women and 38 men), 208 legs (101 right and 107 left) were examined with duplex scanning after clinical examination and diagnosis for venous insufficiency. In all patients, operation strategy was planned before duplex examination. Clinical diagnosis was based on physical examination, Trendelenburg and Perthes' tests and non-directional Doppler. Insufficiency was diagnosed with duplex scanning by a reflux time longer than 0.5 s. There were three groups of legs: primary, secondary and recurrent varicosities. Two areas were distinguished: those in the area of the long saphenous vein (LSV) alone and those in the other areas of the leg, including the area of the LSV. In clinically diagnosed primary varicosities in the area of the LSV ($n = 80$), 58 legs were diagnosed as

having incompetence of saphenous/femoral junction. With duplex scanning, only 47 LSV were thought incompetent. In 22 legs where the saphenous/femoral junction was diagnosed as competent, duplex scanning found 15 to be incompetent. In this area there were no incompetent short saphenous veins (SSV) diagnosed clinically but duplex scanning suggested 17 to be incompetent. Clinically there were no deep incompetent veins, but duplex scanning suggested two. In secondary varicosities in the same area ($n=18$) 14 legs were diagnosed as having incompetence of the LSV, which seemed to be correct with scanning in 13 legs. In four competent LSV this seemed correct in one case. In secondary varicosities there were no incompetent SSV, either clinically or on scanning. In 17 competent deep systems, duplex showed two to be incompetent. In 13 clinically occluded or incompetent deep systems this was proven in only five legs. In 60 patients with recurrent varicosities after surgical treatment, the clinical diagnosis of incompetent LSV seemed to be correct in 25 of 31 cases, and in diagnosis of competent LSV seemed to be correct in 15 of 29 cases. In clinical incompetence of the SSV this was correct in seven of ten veins, and competent SSV was incorrect in 11 of 50 veins. A clinically normal deep system in 57 legs was incompetent in ten with duplex. It was concluded that clinical diagnosis in patients with primary, secondary or recurrent varicosities is inaccurate. For a correct surgical strategy, duplex scanning of the venous system of the leg is essential.

Experimental study of an absorbable Adams de Weese clip

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The efficacy of the Adams de Weese clip has been known for more than 30 years. It is used in young patients to prevent recurrent emboli or prophylactically in certain patients at high risk of embolism. The clip is usually made from Teflon (DuPont) and is thus a permanent implant. For this reason there is unwillingness to advise its use when the risk of embolism is temporary or when the operation is contaminated (e.g. peritonitis). It was thus of interest to develop a biodegradable clip, whose period of efficacy would be predictable.

The new clip has the same shape and size as the Adam de Weese clip. It is made by punch-cutting semicrystalline 2-mm thick sheets of poly- α -hydroxy acid.

The clip has been implanted in five beagle dogs which were examined regularly by laparotomy, radiography of the vena cava and tomography. Cell tissues at the periphery of the clips were examined histologically. Six clips were placed in a subrenal exocaval position. Three control clips were placed on the lower pole of the left kidney. All clips were examined at 3–6-month intervals by laparotomy. Their appearance and integrity persisted for about 9 months. Samples were taken to assess degradation by measuring molecular mass (gel filtration chromatography). After 9 months, the decrease in molecular mass was about 80 per cent. There was no macroscopic reaction around the clip, no thrombosis of the inferior vena cava, and no secondary manifestation. One dog gave birth to three puppies during the experiment.

It is concluded that the filtering effect lasts for at least 9 months, that the clip is resorbed in a period of about 12 months, and that it causes no inflammatory reaction or thrombosis.

Viability of cryopreserved human venous allografts assessed by morphological and tissue culture techniques

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The feasibility of maintaining long-term viability of human venous allografts was assessed. Segments of veins obtained from patients undergoing venous stripping were immersed in 15 per cent dimethylsulphoxide solution, deep frozen at -196°C in liquid nitrogen, and preserved for a period ranging from 1 week to 25 months.

Using scanning electron microscopy, 109 cryopreserved (CP) segments were compared with 17 freshly stripped veins studied within 4 h. There were no differences in endothelial lesions, endothelial loss

or exposure of basement membrane. Using transmission electron microscopy, CP veins were characterized by vacuoles, a thickened and multilamellar basal lamina, and normal mitochondria.

Vein segments of 2 mm² surface area were placed endothelial-side down on a collagen gel substrate in 10 per cent fetal calf serum culture medium. Cell outgrowth was observed in all the non-CP vein segments and seven of nine CP segments within 6–17 days. One month later, cells from both groups were successfully passaged from gels onto plastic plates to form living cultures.

Endothelium for primary tissue culture was digested in a collagenase solution and the cell supernatant seeded on a collagen film in a Petri dish. Confluent monolayers were obtained with non-CP endothelial cells but CP cells did not resist exposure to collagenase.

In conclusion, cryopreservation did not significantly alter morphology or cell outgrowth capacity in tissue explants. However, CP endothelium did not form confluent monolayers on cell culture. Cryopreservation of human venous allografts may be improved if the optimal storage temperature is determined.

Variceal operations using the Várady method and instruments

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Variceal problems are frequently seen in Hungary. Since 1988 the Várady microsurgical method and instruments have been regularly used in this department. Between May 1988 and October 1991, 385 patients underwent operation for varices. Of these, 56 underwent traditional procedures (transection, stripping and excision), 153 had combined transection, stripping and Várady operations, and 176 had Várady operations alone.

Our results with this procedure are demonstrated. Good cosmetic results and a short inpatient hospital stay can be achieved.

Endoscopic ligation of perforating veins of the lower limbs

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A new surgical technique for the treatment of perforating vein incompetence and chronic venous ulceration has been evaluated.

A prospective study of 20 consecutive patients with perforating vein incompetence treated with endoscopic ligation was carried out. All cases were evaluated clinically and with preoperative and postoperative Doppler flow studies.

Obliteration of the incompetent perforator veins was achieved in all 20 patients. No morbidity was encountered and the mean hospital stay was 2.8 days. All patients experienced marked clinical improvement and complete healing of their leg ulcers, when these were present. This technique proved to be safe and reliable in the treatment of incompetent perforating veins of the lower limbs.

Surgeon's effect on wall damage of vein grafts

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Many reports stress the importance of the use of non-touch techniques in dissection and isolation of veins. Clinical trials with different conservation solutions and manipulation methods to prevent endothelial loss during the surgical procedure are numerous. In contrast, the early wall changes after implantation are reported only sporadically. Based on these observations, an investigation was undertaken to evaluate the wall changes in grafts after manipulation and implantation. We studied non-implanted manipulated vein grafts as well as grafts collected from 12 patients who died shortly after coronary artery bypass grafting (CABG). In a 4-year period more than 3200 patients underwent CABG. The wall changes were assessed by light microscopy, immunohistochemistry, and transmission and scanning electron microscopy.

The study demonstrates that preparation with a non-touch technique and conservation of the grafts in heparinized blood is

associated with minimal endothelial cell loss. In contrast, the wall of implanted grafts shows extensive injury; at 12 h after implantation, the vein wall becomes infiltrated with polymorphonuclear leucocytes and within 24 h the endothelium is extensively desquamated. The circular media layer is damaged, resulting in a loss of smooth muscle cells (SMCs). The remaining SMCs switch to a secretory phenotype with a reduced expression for α -SMC actin.

Ischaemia of the media could be a consequence of the interruption of the vasa vasorum and/or wall distension during processing of the graft. These factors nevertheless are inherent to the method of grafting and cannot be controlled.

It is concluded that the surgeon has only a small effect on the cascade of wall transformations and on the conservation of endothelial integrity. In assessment of new therapeutic protocols, antiaggregation therapy, e.g. dipyridamole and aspirin, is essential to prevent deposition of platelets on the extensively damaged wall surface.

Effect of aprotinin on thrombosis in an experimental arterial model

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The serine protease inhibitor aprotinin significantly reduces transfusion requirements during open-heart surgery. However, whether this benefit is associated with an increased tendency to thrombosis has not been studied. The effect of aprotinin in an experimental arterial thrombosis model was investigated. Experiment 1: In 17 male Sprague-Dawley rats, the infrarenal aorta was replaced with a 1.0-mm diameter polytetrafluoroethylene (PTFE) graft of varying lengths. The mean(s.d.) time to graft occlusion, recorded by palpation, Doppler ultrasonography and a distal bleeding test, was 20.2(1.8), 35.8(6.1) and 43.7(6.6) min for grafts of 10, 7.5 and 5.0 mm respectively ($r = -0.98$, $P < 0.05$). Experiment 2: Using this model the effects were investigated of aprotinin (4 mg kg^{-1} intravenous loading dose and $1 \text{ mg kg}^{-1} \text{ h}^{-1}$ infusion) and heparin ($100 \text{ units kg}^{-1}$ intravenous loading dose and $15 \text{ units kg}^{-1} \text{ h}^{-1}$ infusion), singly and in combination on thrombosis (graft length 10 mm).

Group (n = 6)	Time to graft thrombosis (min)	APTT (s)	PT (s)	Bleeding time (min)
Control	20.2(1.8)	17.2(3.3)	21.9(3.0)	2.9(0.7)
Aprotinin	71.7(20.4)*	40.0(15.5)*	29.4(6.2)*	3.0(0.9)
Heparin	118.3(26.4)*†	>300*†	40.7(2.5)*†	22.5(2.3)*†
Heparin + aprotinin	109.5(15.2)*†	>300*†	39.9(14.5)*†	18.9(4.1)*†

Values are mean(s.d.). * $P < 0.05$ versus control; † $P < 0.05$ versus aprotinin. APTT, activated partial thromboplastin time; PT, prothrombin time

This analysis demonstrates that high doses of aprotinin induce a significant anticoagulant effect in this experimental arterial thrombosis model. This effect is less than that seen with heparin alone and is not associated with abnormalities in the bleeding time. The simultaneous administration of heparin and aprotinin does not have a cumulative anticoagulant effect. It is speculated that aprotinin may be the optimal anticoagulant in surgery.

Plantar shear stresses on the diabetic neuropathic foot

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The purpose of this study was to measure the plantar shear stresses on the diabetic neuropathic foot and to compare these with shear stresses on the normal foot.

A low-profile shear transducer has been developed and was used to measure shear stresses. Eight transducers were attached to the plantar surface of the hallux, each metatarsal head and the medial and lateral side of the heel. Ten diabetic patients with neuropathic feet as determined by sensory testing with Semmes-Weinstein hairs walked at 4 km h^{-1} on a treadmill. Three successive readings were

taken from each patient. The results were compared with those obtained from controls matched for age, sex, height and weight.

All the diabetic patients showed increased shear stresses when compared with controls ($P < 0.001$). Increases were most marked in men and over the metatarsal heads.

It is well known that vertical forces are increased in diabetic neuropathy and are important in the aetiology of diabetic neuropathic foot ulceration. The role of shear stress is not clear because of the unavailability of a system for measuring it. It is likely that shear stresses also play a significant role in the development of diabetic neuropathic foot ulceration.

Effect of prophylactic inotropic support on perioperative oxygen flux

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Inadequate tissue oxygenation occurs in the critically ill and carries a poor prognosis. The aim of this prospective randomized study was: first to determine the degree of inadequate tissue oxygenation that occurs during operation in major elective cardiac surgery in patients with normal ventricular function; and second to assess the effect of augmenting haemodynamic indices to 'supranormal' levels on oxygen delivery (D_{O_2}) and consumption (V_{O_2}), and on the degree of inadequate tissue oxygenation that may occur during operation.

Twenty-four patients with ejection fraction 0.5 were randomly assigned to two groups. After induction of anaesthesia, baseline lactate, haemodynamic indices and D_{O_2}/V_{O_2} were measured. The treatment group received a 24-h infusion of doxamine (a vasodilator with positive inotropic activity) at $2 \mu\text{g kg}^{-1} \text{ min}^{-1}$ and controls received saline. Recording continued at preset intervals before and after bypass. Both groups were similar with respect to age, number of grafts and haemoglobin.

Lactate rose significantly in both groups ($P < 0.05$), demonstrating inadequate tissue oxygenation, and persisted over the first 24-h period. However, in patients receiving doxamine support, to achieve haemodynamic indices considered greater than normally required, cardiac index was significantly higher ($P < 0.05$), as were the D_{O_2} and V_{O_2} ($P < 0.05$), than in the control group. This rise in V_{O_2} was associated with an earlier fall in the lactate levels after operation in the inotropically augmented group.

This study demonstrates that inadequate tissue oxygenation occurs in low-risk patients with normal ventricular function undergoing cardiac surgery. It also shows that by deliberately augmenting the cardiac index, and thereby significantly increasing the oxygen delivery and consumption, it is possible to attenuate the perioperative oxygen debt, which should improve postoperative organ function and preservation in patients undergoing major surgery.

Evaluation of cerebral perfusion by ^{99m}Tc HM-PAO brain spectrometry compared with stump pressure

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The assessment of collateral circulation during temporary carotid artery occlusion by various methods generates a great deal of controversy. Intraoperative internal carotid back-pressure, initially described by Moore and Hall¹ in 1969, is nowadays widely used although there is uncertainty as to the real significance of this measurement and whether it can predict tolerance to carotid clamping. In order to evaluate the reliability of this technique, we have compared stump pressure values with cerebral perfusion detected by intraoperative ^{99m}Tc -hexamethylpropylene amine oxime (HM-PAO) brain spectrometry. Seventeen patients, with a mean age of 63 (range 51–75) years, ten men, seven women, suffering from carotid bifurcation lesions, and who had normal basal spectrometry, were studied. All patients underwent carotid endarterectomy, under general anaesthesia, at normocarbina without shunting. In six patients with stump pressure $< 50 \text{ mmHg}$ intraoperative spectrometry demonstrated four severe, one moderate and one mild hypoperfusion, while 11 patients with stump pressure $> 50 \text{ mmHg}$ had normal spectrometry findings in one case and ten had hypoperfusion (four severe, four

moderate and two mild). Stump index in five patients was <33 per cent; in these, intraoperative spectrometry demonstrated three severe, one moderate and one mild hypoperfusion. Only one transient ischaemic attack was observed in the first hours after surgery.

Data reported suggest that stump pressure alone does not accurately represent cerebral perfusion and cannot be considered a reliable method for tolerance evaluation during carotid clamping.

1. Moore WS, Hall AD. Carotid artery back pressure: a test of cerebral tolerance to temporary carotid occlusion. *Arch Surg* 1969; **99**: 702-10.

Ischaemic muscle performance: a new method of assessing peripheral vascular disease

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Muscle performance is a function of blood supply. Its measurement in patients with peripheral vascular disease may reflect the degree of ischaemia better than conventional methods.

Contractions of the affected gastrocnemius, extensor digitorum longus and tibialis anterior (EDL + TA), were separately induced by standardized continuous periods of percutaneous electromyostimulation, pulse width 350 µs, 6 Hz. Muscle performance is expressed as fatiguability index (FI): the ratio of the force of contraction after 5 min to the maximum force of contraction produced. FI, ankle-brachial pressure index (ABPI) and maximum walking distance (MWD) were measured in controls with and without arterial occlusion by thigh tourniquet, in stable claudicants and in patients with critical ischaemia.

Subjects	No. of patients	FI			MWD (m)
		EDL + TA	Gastrocnemius	ABPI	
Control	5	1.00 (0.00) [0.00]	1.00	1.15 (0.10) [0.07]	>250
Control with tourniquet occlusion	5	0.15 (0.05) [0.01]	0.25	-	-
Claudicants	10	0.55 (0.40) [0.015]	0.65	0.77 (0.20) [0.10]	145 (75) [42]
Critical ischaemia	5	0.21 (0.03) [0.01]	0.29	0.20 (0.10) [0.05]	-

Values are mean (range). Values in square brackets are variation of individuals at different days

The reproducibility of FI is high when compared with ABPI and MWD. It also appears to be proportional to the degree of ischaemia. Therefore it may be a better method for assessing limb ischaemia.

Elbow arteriovenous fistulae for haemodialysis

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When no suitable vessels are available in the forearm for the creation of vascular access for haemodialysis, prosthetic grafts are frequently used. However, these devices often require additional surgical procedures to maintain their patency. Therefore, in such cases, it was decided to test arteriovenous (AV) fistulae constructed in the antecubital fossa using the brachial artery and an arm or forearm vein. A total of 272 AV fistulae at the elbow was created, 114 in men and 158 in women. The age of the patients ranged from 17 to 87 years and 59 per cent were older than 50 years of age. In all, 122 fistulae were secondary vascular access procedures and 32 operations failed (11.8 per cent). Among the 240 functioning devices, the overall survival rate was 74.7 per cent at 1 year and 58.4 per cent at 4 years. One fistula is still in use after 12 years. The series includes 44 AV fistulae between the brachial artery and a vein of the forearm, 80 AV fistulae between the brachial artery and the elbow perforating vein, 47 between the brachial artery and the median cephalic vein, and 69

between the brachial artery and a superficial basilic or cephalic vein in the arm. The 4-year survival rates of these fistulae were 51.2, 68.0, 61.3 and 52.7 per cent respectively. The main cause of late failure was thrombosis (73.2 per cent of the failures) followed by insufficient flow (13.4 per cent). Other fistulae were ligated because of infection and pseudoaneurysm formation (11 per cent) or venous hypertension (2.4 per cent). Twenty-seven per cent of the patients had cramping pains in the hand during exercise, but these symptoms were mild and never required closure of the AV fistula. Trophic lesions were not observed. Taking into account the fact that all these patients had vessels of poor quality, the results indicate that elbow AV fistulae provide satisfactory vascular access for chronic haemodialysis.

Maintenance of arterial bypass graft patency: role of a surveillance policy

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During the first year after surgery, 30 per cent of vein grafts develop myointimal hyperplasia causing stenoses which progress to occlusion. Early correction of stenosis should result in fewer secondary reconstructions and amputations, with cost savings.

After arterial reconstruction for critical leg ischaemia, 44 patients (47 grafts) have undergone prospective surveillance by duplex Doppler ultrasonography and ankle-brachial pressure index (ABPI) measurements, 6 weeks after operation and thereafter at 3-month intervals (mean follow-up 11 (range 5-18) months). Intravenous digital subtraction angiography (DSA) was performed after detection of diminished graft blood flow, reduced ABPI or increased peak systolic flow velocity across a stenosis on ultrasonography.

Graft conduits were *in situ* long saphenous vein (30), arm vein (13) or polytetrafluoroethylene (PTFE) (four); 40 distal anastomoses were to single calf or pedal vessels, and seven were below-knee popliteal.

Duplex examination detected 16 stenoses in 13 grafts and one outflow vessel, confirmed by DSA. Clinical observations and ABPI correlated poorly with these findings. Balloon angioplasty was undertaken for 13 stenoses. Three further lesions were corrected by patch angioplasty or arm-vein jump graft. Two cases of progressive inflow disease were treated by common femoral PTFE patch and axillofemoral bypass. Of 16 grafts, 15 remain patent. Only two other grafts have subsequently failed.

Combined duplex/intravenous DSA examination is a sensitive method for detection of graft stenoses. Good results from early intervention suggest that scrupulous surveillance should improve graft patency rates with considerable benefits to patients and overall cost savings.

Long-term clinical and duplex follow-up after proximal vertebral artery reconstruction

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From 1977 to 1989, 28 patients (18 men, ten women), underwent 29 proximal vertebral artery reconstructions. Indications were vertebro-basilar insufficiency in 17 patients, transient ischaemic attacks or stroke in six, and five were asymptomatic. Procedures performed were endarterectomy in 20, reimplantation in five, venous bypass in three and decompression in one case. There was no operative mortality.

Except for one patient from another country, clinical follow-up was complete. Mean follow-up was 85.6 (range 17-146) months. During follow-up ten patients died. Causes included cardiac problems (three cases), carcinoma (three) and stroke (two). Seventeen patients were alive, 13 without cerebrovascular symptoms, while two had sustained a hemispherical stroke, one was only slightly improved and one had had a drop attack 131 months after operation. The 5- and 10-year actuarial survival rates were 85 and 51 per cent, respectively.

Follow-up data with duplex scanning were available in 26 patients and were complete in 24. Mean duplex follow-up was 78.6 (range 3-146) months. Significant abnormalities were noted in six patients, only one of whom was symptomatic. Mean time to restenosis was

77.3 months. Late angiographic findings in ten patients correlated well with duplex findings.

Duplex scanning is a useful tool in the follow-up of patients who undergo proximal vertebral artery reconstruction.

Autologous predonation and intraoperative blood salvage in elective aortic aneurysm repair

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Blood replacement in abdominal aortic aneurysm (AAA) surgery places demands on blood bank resources and exposes patients to the risks of transfusion. This study assessed the feasibility of elective AAA repair without homologous transfusion, using only predonated autologous blood and intraoperative blood salvage.

Twenty consecutive patients were evaluated. Five were excluded according to protocol criteria. Fifteen patients each donated 1 unit of blood at 14 days, 7 days and immediately before operation. Blood shed during operation was salvaged using the Haemonetics Cell Saver-III system. After operation, homologous blood was to be transfused if the haemoglobin (Hb) fell below 9 g dl^{-1} .

Aneurysm size ranged from 5.2 to 8.4 cm in diameter. A mean (s.d.) volume of 1180 (220) ml of blood was predonated by each patient without complication. Mean (s.d.) intraoperative blood loss was 840 (340) ml, with a mean (s.d.) of 260 (195) ml salvaged during operation. Mean (s.d.) Hb was $13.2 (1.5) \text{ g dl}^{-1}$ before operation and $10.9 (1.5) \text{ g dl}^{-1}$ on the first postoperative day. The first two patients were mistakenly transfused with banked blood in breach of the protocol, while the predonated blood from two other patients was discarded owing to repeated postponement of operation. The remaining 11 patients have not required homologous transfusion. We conclude that elective AAA repair can be performed safely without the use of homologous blood.

Familial abdominal aortic aneurysm

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Although aneurysms of the abdominal aorta (AAAs) are a common pathology in the elderly, familial clustering of cases has only recently been noticed. Since the first case reported by Clifton¹ (1977) several series have been published by a small number of teams, confirming the initial impression and suggesting that AAA is frequently familial. Although descriptive statistics are readily available on sex ratio, relative rates for sibs and on the natural history of the disease, pathogenicity and genetic background remain obscure. The mode of inheritance (dominant, recessive, X-linked, multifactorial) remains uncertain.

We recently decided to initiate a combined retrospective and prospective study on AAA, based on the surgical population of our University Hospital. The data collected here represent the preliminary results of this on-going research project.

Between January 1976 and December 1990, 789 patients have been surgically treated for asymptomatic, symptomatic non-ruptured or ruptured AAA in our department (500 of them during the past 5 years). Ascertainment of familial cases was done primarily by retrospective review of hospital files. The first 300 patients' files yielded 24 positive histories of AAA (8 per cent). Patients of this group (or their surviving partners) were interviewed by telephone for confirmation of the data and construction of pedigrees.

Twenty-four families have been analysed. In families with AAA, the total number of affected patients is 54. AAA was found in 17 of 85 siblings (20 per cent) and ten of 48 parents of the probands (21 per cent). Rupture occurred in 14 (26 per cent). Mean age of presentation is 64.4 years for the probands. Twelve families showed a horizontal distribution of the cases, with AAA limited to one sibling. In ten families, AAA was present in two successive generations. In one case AAA in three generations was likely but not proven. The last family is represented by two first cousins. In all cases but one, when two generations were involved, the proband was an offspring. Four of five women were mothers of probands. The sex ratio (male:female) was 9.8:1.

The patients with positive family history are younger than non-familial patients (mean (s.d.) age 64.4 (9.4) versus 67.7 (9.2)

years). The rate of rupture is higher (14 of 54; 26 per cent) in the familial patients when compared with non-familial patients (32 of 276; 12 per cent) ($P < 0.001$). Our data confirm the higher risk of rupture of AAA in familial cases and support the need for a systematic ultrasonographic screening policy in first-degree relatives of AAA patients.

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Critical limb ischaemia and electrical spinal cord stimulation

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Improved vascular techniques and an aggressive surgical approach have contributed to increased foot salvage in patients with ischaemic rest pain, non-healing ischaemic ulcers or gangrene. However, the treatment of infrainguinal bypass failures remains a difficult problem and optimal management has been controversial. It has to be emphasized that major amputation in the medically compromised patient with severe limb ischaemia has a significantly higher operative mortality rate than vascular reconstruction. Epidural spinal cord stimulation (ESCS) has been suggested as an alternative treatment in patients with severe limb ischaemia in whom vascular reconstruction is not possible. We studied the effects of ESCS on microcirculatory blood flow in 17 patients with ischaemic rest pain and ulcers. Angiography demonstrated occluded crural arteries technically unsuitable for reconstructive surgery.

All the patients had intolerable unilateral rest pain and eight of them had non-healing ischaemic ulcers. All the patients experienced improvement of pain. Trophic ulcers disappeared in five and were reduced in size in another three patients. During the follow-up period, amputation was necessary in two patients. Some parameters were assessed before and after ESCS: these were Doppler ultrasonography, strain gauge plethysmography, temperature measurement, radionuclide angiography and somatosensorial evoked potential. The parameters showed an increase of peripheral circulation in 13 patients. Insufficient experimental and clinical data are currently available to recommend ESCS as the treatment of choice in patients with critical limb ischaemia, but it may be considered as an alternative treatment in patients with critical limb ischaemia in whom vascular reconstruction is not possible.

Five years' experience with homologous saphenous vein grafts in infragenicular limb revascularization

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A retrospective review of patency of infragenicular limb revascularization with the use of homologous saphenous vein grafts (HSVG) is reported.

From November 1986 until December 1991, 49 infragenicular limb revascularization procedures were carried out under general anaesthesia with the use of HSVG in 44 patients of mean age 72 (range 53-90) years. There were 22 men and 22 women. Most of these patients had Fontaine Class III or IV limb-threatening ischaemia and poor run-off (Harvard II or III) on below-knee angiography. Many had undergone previous revascularization or arterial procedures, or had used poor quality autologous saphenous veins, and were poor surgical risks.

There were three postoperative deaths (<1 month) with functioning bypasses and five deaths (>1 month) in the follow-up period (three with a functioning bypass). Nine of the 44 patients (20 per cent) had definitive graft thromboses, seven resulted in knee or thigh amputation. Six, 12 and 24 months total cumulative uneventful patency was achieved in a mean (s.d.) of 84(6), 75(8) and 64(10) per cent of cases respectively.

In conclusion, the use of HSVG is a good technical procedure for limb salvage in a selected high-risk group of patients with absent or unusable autologous saphenous veins. The patency rates are acceptable and general anaesthetic time is considerably reduced in these poor-risk surgical patients.

Endovascular arterial reconstruction using a new superpulsed neodymium yttrium–aluminium–garnet laser

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A new method of endovascular peripheral laser angioplasty has been developed and used for iliac and femoropopliteal arterial recanalization. It consists of a neodymium yttrium–aluminium–garnet (NdYAG) laser that is specially superpulsed. The superpulse consists of a train of short pulses, length 1–2 μ s for the individual subpulses and 500 μ s for the whole pulse train. The peak power of the main pulse is approximately 250 W and the amplitude of the following pulses decreases steadily. The pulse rate is 1000 Hz.

A miniplasma effect, created between the 320- μ m diameter fibre end and the calcified plaque, increases the effect of the low-energy beam. Used as the primary treatment of calcific lesions, the superpulse laser improves the results of arterial recanalization, particularly with the use of the contact YAG sapphire.

Clinical use shows the efficiency of such a procedure for arterial recanalization. The preliminary results emphasize the interest in associating balloon angioplasty and stenting with arterial recanalization.

Dynamic three-dimensional visualization of velocity profiles downstream of graded stenoses on the abdominal aorta in pigs

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In order to investigate local haemodynamics at arterial stenoses a perivascular multielement Doppler ultrasonographic transducer was used for registration of velocity fields and estimation of turbulent stresses downstream of smooth, graded stenoses on the abdominal aorta in pigs.

Axisymmetrical stenoses of varying degrees (defined as internal vessel area reduction) were applied in six pigs on the infrarenal abdominal aorta exposed retroperitoneally through a midline laparotomy. Point blood velocities were registered by a 10-MHz pulsed Doppler flow meter employing a modified zero-crossing detector with a multielement Doppler transducer equipped with five single probes. This enabled point blood velocity measurements in a plane perpendicular to the flow axis along one diameter from the anterior to the posterior vessel wall at three poststenotic positions. Signal analysis included ensemble averaging, turbulence analysis and three-dimensional visualization of velocity profiles.

Downstream of minor (< 40 per cent) and moderate (40–65 per cent) degrees of stenosis the velocity profiles were nearly parabolic with diastolic flow reversal at the posterior vessel wall. Immediately downstream of severe (> 65 per cent) stenoses a prominent poststenotic jet and systolic recirculation zones were present. Further downstream vortices and eddies dominated the flow field. Turbulent energies were most pronounced corresponding to the high velocity jet and at locations with high velocity gradients.

In conclusion, the present study demonstrated that pulsed Doppler ultrasonography, employing a zero-crossing detector, is able to register flow phenomena such as jet-like flow, coherent structures, vortices and recirculation zones in the poststenotic flow field.

Effect of regional lymphatic stimulation on healing of experimental varicocele

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In the course of treating surgically induced experimental varicocele in 60 Wistar rats by means of regional lymphatic stimulation, it was observed that haemodynamic metabolic failure in the region of the left renal vein resulted in apparent changes of the intratesticular circulation of lymph by the 14th postoperative day. The morphological signs of lymphatic stasis increased up to the 30th postoperative day.

The rats which were given three single intratesticular injections of the lymph stimulating drugs showed, on the 15th, 16th and 17th days, marked lessening of the tissue oedema in both experimental groups.

The elimination time of the methylene blue (0.2 ml of a 0.5 per cent solution) from the testis (normal mean 248(30.3) s) and from the epididymis (normal mean 423(85.8) s) was increased 1.7 times in the first experimental group and 4.2 times in the second one.

This was normalized completely after lydase injections (0.5 ml of a 0.16 unit ml⁻¹ solution) by the end of the 60th postoperative day, while novocaine (0.5 ml of a 0.25 per cent solution) had only a partial ameliorating effect.

Renal cortical blood flow recorded by laser Doppler flowmetry

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A preliminary report is made of renal cortical perfusion recorded by laser Doppler flowmetry, a new technique for assessing the microcirculation. A comparison was made between basal flow and the effects of renal clamping and declamping.

Twenty Wistar rats were studied. In each case the optical fibre was implanted in the ventral surface of the left kidney. Basal blood flow was then recorded for 10 min, followed by clamping of the abdominal aorta immediately before the root of the renal artery; after 1 min of clamping, the abdominal aorta was unclamped – the recording obtained reflected both actions. A Periflux PF3 flowmeter was utilized. The technique is based on the fact that monochromatic light transilluminating a tissue is spectrally backscattered by moving red blood cells.

The Table shows perfusion units, total backscattered light and red cell concentration in mean(s.d.) values. Clamping of the abdominal aorta reduced renal blood flow to 71 per cent with respect to the basal values, as reflected by the laser Doppler technique; flow values recovered following unclamping. In spite of clamping of the abdominal aorta a slight renal cortical capillary bed flow persisted, corresponding in part to small movements by cells trapped within the capillary lumen. Thus, zero occlusion level does not coincide with a biological occlusion. When the abdominal aorta was unclamped, a reactive hyperaemia was noted, with values in excess of 40 per cent over basal for a period of several minutes; following this, flow returned to normal.

	Maximum	Minimum	Mean
Perfusion units	44.13(5.24)	21.80(3.29)	32.95(3.55)
Backscattered light	2.06(0.27)	1.89(0.25)	2.00(0.26)
Red cell concentration	119.25(15.60)	54.34(11.65)	71.44(12.92)

Values are percentages

These experiments in the rat suggest that laser Doppler flowmetry of the kidney surface clearly reflects relative changes in kidney blood flow in this experimental model.

New vena cava filter (Opcetra): an experimental study

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This study was designed to evaluate the efficiency of the Opcetra filter, both *in vitro* and *in vivo*.

An *in vitro* study compared the Opcetra, Greenfield and LGM filters. Filters were placed sequentially in a constant flow of 2.5 l min⁻¹ water:glycerin (60:40 per cent). Blood clots of 7, 5 and 3 mm in diameter were injected through a side port. Each filter was exposed 50 times to clots of each size.

Diameter of clot (mm)	Percentage capture (<i>in vitro</i>)		
	Opcetra	Greenfield	LGM
3	66 (33)*	34 (17)	50 (25)
5	100 (50)	82 (41)	100 (50)
7	100 (50)	100 (50)	100 (50)

Values in parentheses are the actual number of times the clot was captured. * $P < 0.003$ versus Greenfield (Fisher's exact test); no other differences were significant.

In the *in vivo* study, an Opcetra filter was introduced under general anaesthesia percutaneously via the right jugular vein into the inferior vena cava in ten sheep. Sheep were followed up for periods of 40 or 98 days. A control radiograph and cavogram were obtained after filter placement. Clot embolization with blood mixed with barium powder was performed through the femoral vein. In group 1, embolization was performed after 40 days, and sheep were killed immediately. In group 2, embolization was carried out after 90 days, and sheep were killed 8 days later for histological study of the vena cava wall.

In the *in vivo* study, one sheep died on induction of anaesthesia. Nine filters were easily implanted. Radiography and cavography confirmed good filter position, its satisfactory opening, and the absence of tilting. No migration was noted in group 1 (three sheep) or group 2 (six sheep). All clots embolized through the right femoral vein were trapped in the filter (radiography of controls, after embolization, and before killing). Anatomopathological evaluation confirmed clot capture and showed that some hooks had transfixed the wall of the vena cava, but without perivenous haematoma; adjacent structures were undamaged.

These encouraging results must be confirmed by a human multicentre study.

Duplex assessment of clinically diagnosed venous insufficiency

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In a prospective study in patients with varicose veins, the impact of duplex scanning was compared with physical examination combined with continuous-wave (CW) Doppler flow measurements. Duplex examination was performed in a vertical position with examination of the long saphenous vein (LSV), short saphenous vein (SSV), deep venous system and perforators. A reflux time exceeding 0.5 s was scored as abnormal.

On clinical and CW Doppler grounds, 208 legs were classified as primary, secondary or recurrent varicoses and identified as having insufficiency of the LSV, SSV and/or the deep system. Results were compared with the duplex findings.

Our results showed that in primary LSV insufficiency the clinical and CW Doppler diagnosis was false-positive in 14 of 75 legs and false-negative in 27 of 51 legs. In secondary LSV insufficiency the false-positive rate was one of 14 and the false-negative three of four legs. In the LSV group the clinical classification of the deep system was also incorrect in five of 98 and the classification of the SSV was incorrect in 17 of 98 legs.

In the clinical SSV group the false-positive rate was six of 32 and the deep system was incorrectly diagnosed in eight of 13. In 60 legs with recurrent varicoses, insufficiency of the LSV was correctly diagnosed in 25 of 31; however it was incorrectly classified in 14 of 29. In this group the data for SSV were false-positive in four of ten, false-negative in 11 of 50, and for the deep system the false-positive rate was two of three, and the false-negative rate ten of 57.

In conclusion, duplex scanning proved to be superior to clinical examination including CW Doppler flow measurements in assessing venous insufficiency.

Fully implantable venous access systems

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The chemotherapeutic treatment of the cancer patient raises, among other questions, those of the choice and maintenance of a vascular access for the administration of drugs. Central access systems, such as Hickman-Broviac catheters, have represented a considerable step. They are, nevertheless, associated with a high rate of sepsis and thrombosis which limits their use. To avoid these complications, totally implantable vascular access systems were devised.

In the present work, our experience of the utilization of those vascular access systems is reported. Since 1986, 185 reservoir pumps have been implanted. Two types of reservoirs have been used: Implantofix by percutaneous cannulation of the subclavian vein in

130 (70 per cent) patients, and Port-a-Cath by surgical exposure of the external jugular vein in 48 (26 per cent) cases. Other types of catheters were used in the remaining seven (4 per cent) patients.

The mean(s.d.) number of days of use of the reservoirs was 290(210). The mean(s.d.) number of punctures made was 390(120). The total number of complications was 20 (11 per cent).

Comparisons are made of the technical difficulties of placement, the mean time taken for insertion, the aesthetic as well as functional result, and the surgical complications of each system.

Use of venous allografts in hepatobiliary surgery

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The use of artificial conduits (GORE-TEX or Dacron) as interposition or bypass grafts in the portal venous system is associated with high rates of early thrombosis. The use of homologous veins (such as the internal jugular vein) adds a further operation to what is already a long procedure. Preserved iliac veins, harvested from organ donors, are used infrequently in graft recipients and so provide a ready supply of venous allografts for use in other circumstances.

We have used such allografts in seven patients, five for replacement of a portal vein resected *en bloc* with an invading cancer (pancreatic cancer, two cases; bile duct cancer, three cases; all with partial liver resection) and two for complicated cases of portal hypertension. The median preservation time for the vein graft before insertion was 6 (range 1–29) days. No patient received immunosuppressive treatment and all patients survived operation and left hospital. In two patients the graft apparently functioned initially but later thrombosed; in the remaining patients, the clinical course suggests that the grafts have remained patent. The longest follow-up at present is 20 months.

If venous allografts used without immunosuppression prove to retain patency over the long term, then the indications for their use may become wider and more varied.

Iliac artery obstructive disease after kidney transplantation

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Aortoiliac obstructive arterial disease can cause intermittent claudication. In renal transplantation an iliac artery stenosis proximal to the renal artery anastomosis may jeopardize renal function and cause hypertension. To determine the localization of stenoses we performed echo Doppler studies in three recipients of a renal allograft in whom there was suspicion of aortoiliac obstructive disease. In all patients intermittent claudication was the initial complaint. During ultrasonography Doppler spectra from both femoral arteries and from arteries of the renal allograft were obtained.

In the first patient only the Doppler spectrum of the leg ipsilateral to the allograft was abnormal. Ankle:brachial pressure index (ABPI) was 0.61 and renal function remained stable. In the second patient, Doppler spectra in the renal arteries and the ipsilateral femoral artery were poststenotic immediately after transplantation. ABPI was 0.58. Arterial digital subtraction angiography showed a dissection of the iliac artery, which was indeed located proximal to the arterial anastomosis. Renal function, however, remained stable and walking distance gradually increased. In the third patient poststenotic spectra were seen in the renal arteries and in the ipsilateral femoral artery. ABPI was 0.57. Increasing hypertension and deterioration of renal function necessitated intervention. Femorofemoral bypass was performed successfully. Serum creatinine levels dropped from $177 \mu\text{mol l}^{-1}$ before surgery to $123 \mu\text{mol l}^{-1}$ the day after and infrarenal Doppler spectra normalized. Intermittent claudication disappeared.

In conclusion, iliac artery obstructive disease has an extra dimension in renal transplantation. Localization of the stenosis is essential for the choice of treatment. Doppler ultrasonography can localize these iliac artery stenoses.

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Editors' announcements

Dual publication – again

Another case of dual publication has come to the Editors' attention, as follows:

Kent P, Ashley S, Thorley PJ, Shaw A, Parkin A, Kester RC. 24-Hour survival of autotransfused red cells in elective aortic surgery: a comparison of two intraoperative autotransfusion systems. *Br J Surg* 1991; **78**: 1473–5.

Thorley PJ, Shaw A, Kent P, Ashley S, Parkin A, Kester RC. Dual tracer technique to measure salvaged red cell survival following autotransfusion in aortic surgery. *Nucl Med Commun* 1990; **11**: 369–74.

The data contained in the two papers are essentially identical. Letters requesting an explanation were sent to the corresponding and senior authors of the *Br J Surg* version, but no reply has been received. One of the other authors wrote spontaneously denying any knowledge of the *Br J Surg* submission, yet a signature was included against this author's name in the covering letter that accompanied that submission. This experience serves to illustrate why we insist on the signatures of all authors in such covering letters.

The Editors' dislike of dual publication was spelled out in a similar announcement earlier this year (*Br J Surg* 1992; **79**: 3). Dual publication has been observed to occur in other journals and may be on the increase (*BMJ* 1992; **304**: 1029). We regret that it is necessary to reiterate that authors who indulge in this practice put acceptance of any further manuscripts in jeopardy and warn that we are actively considering the introduction of spot checks of accepted articles against literature databases.

Case reports

The Editors like to have a sprinkling of Case Reports in the Journal, although restrictions on space mean that the acceptance rate for these is lower than for any other type of article. Authors are welcome to submit reports of a case or cases, and those of sufficient interest or novelty may be sent to one referee for an opinion. We would like to draw attention to the tightening of regulations for Case Reports. They should not exceed 500 words and may contain no more than five references and one illustration. Similar restrictions apply to Short Notes and Surgical Workshops – please refer to the Instructions to Authors. Those submitting such papers are strongly advised to conform to these guidelines.

R. C. N. Williamson
J. R. Farndon
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Company Secretary

PROFESSOR DAVID CARTER



David Craig Carter is Regius Professor of Clinical Surgery in the University of Edinburgh and a consultant surgeon at Edinburgh Royal Infirmary. Born in 1940, he qualified from St Andrew's University in 1964 and obtained his Edinburgh Fellowship 3 years later. His early postgraduate years were spent working for a series of knights: Sir Ian Hill at Dundee, Sir John Bruce and Professor (later Sir) Patrick Forrest at Edinburgh, and then Sir Ian Macadam at Makerere University, Kampala, Uganda. In 1974 he was appointed Wellcome Trust Senior Lecturer at Edinburgh, and in 1976 was seconded for a year to work with Dr W. P. Longmire and the late Dr Morton Grossman at the University of California, Los Angeles. He was awarded an MD at Dundee in 1979. David Carter was appointed to the St Mungo Chair of

Surgery in the University of Glasgow at Glasgow Royal Infirmary in 1979 before returning to Edinburgh in 1988. His clinical interests are in upper gastrointestinal and HPB surgery, particularly peptic ulcer disease, portal hypertension and pancreatitis. Distinctions too numerous to list include invited lectures and visiting professorships in the USA, Australasia, South Africa, Hong Kong and several European countries. He edits *Rob and Smith's Operative Surgery*, chairs the Scottish Committee for Postgraduate Medical Education, acts as Secretary of the James IV Association of Surgeons and is a past Secretary of the Surgical Research Society. He was Co-Editor of *The British Journal of Surgery* for 5 years from 1986 and in 1991 became Company Secretary of the BJS Society.

Treasurer

TOM BATES



Tom Bates was born in 1942. He qualified at St Bartholomew's Hospital, London, in 1966 and worked as a house surgeon to Sir Edward Tuckwell at Bart's. There followed a series of training posts in and around London, including periods as surgical registrar at the Luton and Dunstable Hospital and St Olave's Hospital. He obtained his FRCS Diploma in 1971. He became a senior registrar at Guy's Hospital in 1973, and within this post worked on the Guy's Breast Unit, at the Hospitals for Sick Children, Great Ormond Street, and as a lecturer in the University Department of Surgery at Guy's, where he carried out research on intestinal adaptation with Professor Hermon Dowling. Tom Bates was appointed a consultant surgeon at the William Harvey Hospital, Ashford, Kent, at the early age of 33 years. His clinical and academic interests are concentrated on carcinoma of the breast, the epidemiology and treatment of gallstones, and the prevention of wound infection. He has served as Regional Adviser in Surgery (South-East Thames), Secretary to the Surgical Section of the Royal Society of Medicine and President of the Harveian Society. He joined the Specialist Advisory Committee in General Surgery in 1989 and has just become its Vice-Chairman. In 1987 he joined the Council of The British Journal of Surgery Society and in 1992 has been appointed Treasurer.

Vice-Chairman (Elect)

PROFESSOR NORMAN WILLIAMS



Norman Stanley Williams (born 1947) is Professor of Surgery in the University of London at the Royal London Hospital and an honorary consultant surgeon both there and at St Mark's Hospital, London. He trained at the London Hospital (then without its royal appellation) and qualified in 1970. There followed a series of posts at the London and associated hospitals as house officer, senior house officer and registrar, culminating in his FRCS in 1975. Thereafter he worked in Bristol before becoming Lecturer in Surgery with Professor David Johnston in Leeds. Following a year in Dr Morton Grossman's laboratory in Los Angeles, he obtained a London MS degree in 1982. Norman Williams became Senior Lecturer in Leeds in 1982 and was appointed to the Chair of Surgery at the Royal London in 1987. He is primarily a coloproctologist, though his substantial corpus of published work includes papers on many different aspects of surgical gastroenterology. Distinctions include the Patey Prize (Surgical Research Society) and the Moynihan Fellowship (Association of Surgeons). He is in demand as a lecturer and visiting professor and has travelled widely during the past 6 years. He joined the Editorial Committee of *The British Journal of Surgery* in 1985, representing the Surgical Research Society for the first 3 years, and he takes over from Mr Brendan Devlin as Vice-Chairman of the BJS Society later this year.

Robin Williamson

Vanishing bile duct syndrome

An important endpoint for numerous pathological processes affecting the hepatobiliary tree is destruction of the biliary apparatus, leading to its disappearance either focally or diffusely within the liver. Careful examination of portal tracts fails to reveal a normal complement of bile ducts, and cholestatic clinical features develop. If loss is extensive, diminished life expectancy is inevitable. The syndrome of vanishing intrahepatic bile ducts (VBDS) may be caused by developmental, immunological, vascular, infective or chemical mechanisms.

Congenital malformations present as *neonatal cholestatic syndromes* which used to be thought of as atresia of the intrahepatic bile ducts. The present concept, however, is no longer that the bile ducts are unformed, but rather that, at some moment during their embryonic development, they are damaged by an unknown agent and progressively destroyed¹. There may be the appearances of atresia when all ducts are missing or an intermediate stage of 'paucity of intrahepatic bile ducts' (PIBD) when the number of ducts is drastically reduced. When associated with other congenital malformations (including postvalvular pulmonary stenosis), a characteristic facial appearance and a familial incidence (syndromatic PIBD), the chronic cholestasis is only mildly fibrogenic and neither cirrhosis nor secondary portal hypertension is observed². In non-syndromatic PIBD the following have been demonstrated in different cases: cytomegalovirus; rubella; reovirus 3; α_1 -antitrypsin deficiency; and an increase in trihydroxycoprostanic acid level. The prognosis is poorer with half of the patients dying from liver failure in the first years of life.

Diseases in which destruction and disappearance of bile ducts may occur in later life are primary biliary cirrhosis, primary sclerosing cholangitis, sarcoidosis, mucoviscidosis, suppurative cholangitis (and Caroli's disease), liver transplant rejection, graft *versus* host disease, histiocytosis X, Hodgkin's disease, chronic drug-induced cholestasis, and sclerosing cholangitis complicating intra-arterial infusion of chemotherapeutic agents. Immunological mechanisms are clearly implicated in the obliterative inflammatory process in several of these conditions, although the initiating event may be obscure.

In *primary biliary cirrhosis* the bile duct lesions are focal and confined to the interlobular bile ducts with a calibre of 50-100 μ m. Ninety per cent of patients are women and almost all have antibodies to mitochondrial enzymes, including pyruvate dehydrogenase. Bile duct destruction appears to be mediated by cytotoxic lymphocytes which surround and invade the wall of the bile duct. Increased class II human leucocyte antigen (HLA) expression on the bile duct cells has been reported, and the disease may represent a failure in immunoregulation with a loss of tolerance to tissues bearing a rich display of major histocompatibility complex (MHC) antigens.

The implication of cell-mediated immunity directed by, or targeted at, MHC antigens displayed on biliary epithelium is strengthened by the association of VBDS with both liver allograft rejection and chronic graft *versus* host disease following allogeneic bone marrow transplantation. On liver biopsy portal tracts normally contain an identifiable bile duct of approximately the same size as the arteriole. In liver allograft rejection, VBDS is suggested when bile ducts are present in fewer than half of the portal tracts, but, because of sampling error, it is wise to be cautious about this diagnosis unless other features are present or progressive changes are seen on subsequent biopsy. Biopsy specimens reveal destructive cholangitis, ductopenia and, eventually, 'burnt out' portal tracts devoid of inflammation because the bile ducts (the target antigens) have disappeared. VBDS may present abruptly soon after transplantation or after a period of normal graft function. More often the onset is insidious, with a slowly progressive deterioration in liver function. When immunosuppression after transplantation is less than therapeutic, the risk of developing VBDS is especially high. The incidence of VBDS is currently 8-15 per cent in most liver transplant series and when advanced it is fatal without retransplantation. It represents a cardinal feature of chronic rejection and the terms are sometimes used interchangeably, although it can be difficult to determine the point of irreversibility. Hubscher *et al.*³ recently described six patients in whom VBDS after liver transplantation appeared reversible.

HLA antigens has not yielded consistent results. In one study VBDS associated with class I mismatch, class II match and cytomegalovirus infection; in another, a positive lymphocyte crossmatch and a class II mismatch, in particular DR disparity, was found. There is, therefore, insufficient evidence to suggest that HLA matching or deliberate mismatching would improve liver graft survival⁴⁻⁷.

Primary sclerosing cholangitis is a disease of unknown aetiology and pathogenesis which usually involves the entire biliary tract and is best diagnosed by endoscopic cholangiography. Segmental narrowings give a beaded appearance. In about 70 per cent of patients there is a coincident history of ulcerative colitis and either condition may appear first in a given patient. This suggests that the colon and bile ducts share a common predisposition to an inflammatory condition, rather than that one condition leads to the other. In primary sclerosing cholangitis and autoimmune chronic active hepatitis there is an increased prevalence of HLA-B8 and HLA-DRw3.

Infection with cytomegalovirus or *Cryptosporidium* has been seen to cause progressive mucosal irregularity and ultimate destruction of bile ducts in the acquired immune deficiency syndrome⁸. Intra-arterial chemotherapy with floxuridine, and intrabiliary spillage of formaldehyde and sodium chloride in the treatment of hydatid disease of the liver, have also produced sclerosing cholangitis. Chlorpromazine and flucloxacillin can cause cholestatic jaundice persisting for more than 6 months during which VBDS may be severe.

Both intrahepatic and extrahepatic segments of the biliary tree may be involved by conditions causing VBDS, but they are not generally associated with surgically correctable causes, and the extrahepatic biliary tree may be normal. Because of its frequently progressive course and potentially fatal outcome, both prevention and early recognition of the syndrome are vital, the latter to establish aetiology and allow an appropriate course of management.

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Improving practice: the clinician's role

Countries throughout the western world are re-examining the structure of healthcare systems, motivated mostly by cost issues. Why are we spending so much on healthcare? Is it costing us too much? Are we getting sufficient value (i.e. additional health) for each pound invested? How can we save money or at least control the increase in healthcare expenditure?

Such issues are often the purview of economists, administrators, and planners. It is not surprising, therefore, that responses take the form of economic or administrative solutions. Thus, in the US fee-for-service system, patients are required to pay an increased percentage of the bill. Canadian policy-makers examine health maintenance organizations in the US for their relevance to Canada. The UK adopts competitive strategies at least partially developed by an American economist. Meanwhile, US legislators examine European systems to see how their own costs can be contained. The Mad Hatter in *Alice in Wonderland* certainly would have enjoyed the show.

The fundamental problem with all of these solutions when they work (i.e. save money) is that they can be dangerous (people may be killed). Economic solutions that are devoid of clinical input virtually never help to achieve what should be the goal of every healthcare system – to deliver medically necessary care to everybody. 'Necessary' care here means that which is appropriate (i.e. the improvement for the patient exceeds the risk), and the associated benefit is not trivial. In addition, physicians would become upset if the health system in which they worked did not permit them to offer their patients such a service; they might even be liable if they did not recommend the use of this service to their patients.

Are the above assertions supported by scientific evidence? In a randomized controlled trial, it has been demonstrated in the US fee-for-service system that making a patient pay something towards medical care reduced use by 40 per cent, relative to a system that was free at the point of delivery¹. However, use of medically appropriate services declined as quickly as that of inappropriate ones². In the UK, budgeting has no doubt decreased use; rates of coronary artery bypass surgery are less than one-fifth of those in the USA³. However, even in the face of rationing of effective services, it has been demonstrated that a large percentage of coronary artery bypass operations carried out in the Trent Region of the UK were performed for medically equivocal (benefit and risk to patient about equal) or inappropriate reasons⁴. A review of the English language literature⁵ suggested that one-quarter of what physicians do to patients could have been omitted without causing the patients' health to worsen. On the other hand, when a 'meat axe', non-clinical, approach to reducing such use is introduced as health policy, as occurred in California by altering the insurance status of poor, medically indigent adults, such a change produces many unnecessary deaths⁶.

So what must we do as physicians? First, we must acknowledge the public's right to clinical accountability for the resources it devotes to healthcare; society has a legitimate right to control healthcare expenditure. Second, we must make the public aware that a non-clinical approach to controlling healthcare costs will not change the distribution of necessary as opposed to unnecessary care; it may also kill people. Third, the only way to improve substantially the relationship between the resources expended on healthcare and the resultant health of patients is for physicians to take the lead in defining explicitly the necessary care that should be provided with public funds. Fourth, we must provide clinically detailed data to the public on the extent of underuse and overuse. Fifth, we must be prepared to work with economists and planners to develop joint clinical and economic solutions, allowing the removal of unnecessary treatments while ensuring that necessary care is provided to everybody.

To achieve this, physicians must develop explicit clinical standards of the necessity for the most common procedures and services. This will require use of a method combining a literature analysis with expert judgement⁷. In doing this, the following principles must be kept in mind. The standards must be clinically detailed; as many as 3000 different scenarios may be needed to describe all the potential uses of coronary artery bypass surgery. The literature review must be taken seriously and should be led by a clinician with health service or epidemiological training. A single medical or surgical society should not set its own standards; multiple specialties must be involved, or results will be biased. The standards should be made publicly available and they should be used by physicians and patients before the receipt of a major

Study of M.M.I. requires the development and installation in the physician's office of a computer system to produce a 'necessity score' before receipt of a procedure. In another score would serve two purposes. It would define which services, subject to a HLA appeal, would be covered or paid for out of public money. It would also that be a starting point for the patient and physician for the development of a diagnostic and therapeutic plan. There may be instances in which a patient might want something that will not be funded by public money; he or she would then need to pay for that chosen privately. On the other hand, clinically justifiable exceptions would be approved for payment, and data on them would be fed back to the guideline developer along with newly developed research information to allow continuous updating and improvement of standards.

Those who oppose such a development argue that more information is needed about what does and does not work (i.e. more randomized trials must be performed) before this process can begin⁸. Others are worried about clinical freedom⁹. Although both of these concerns are legitimate, it must be recognized that, no matter how much money is invested in clinical research, physicians will never know as much as they would like to and will always be practising in a state of relative ignorance. This level of uncertainty, however, should not prevent physicians from making their best attempts to decide what currently should and should not be done. Such an effort will also lead to development of a better research agenda that properly reflects the needs of practitioners. To prevent the stagnation of medicine, standards must be updated as new information becomes available. Finally, there is no better place to begin efforts at improving quality than in setting standards for necessity of care. Before worrying about how well a procedure is performed, or how satisfied a patient is with his or her care, should physicians not be concerned about whether people who really need a procedure obtain it, and whether those who actually get treatment really require it? Health delivery systems may change radically in the next decade. It is to be hoped that clinicians will realize that only by developing and applying standards of care will such systems perform better. Methods of developing standards exist; they must begin to be applied and improved. We can help society achieve its goal of delivering all necessary care to everybody if we have the will.

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Prognostic factors in cancer

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Colorectal carcinoma is the second commonest cause of death from cancer in western countries, accounting for 14 and 16 per cent of cancer deaths in men and women, respectively¹. Approximately one person in five in England and Wales now dies from cancer, and one in eight of these will die from tumours of the large bowel².

A clinician encountering a patient with colorectal cancer needs to know the expected outcome to plan appropriate therapy. Over the past 60 years, claims have been made of numerous variables being related to survival. However, the application of many of these in a clinical context has serious drawbacks, in that they are complex, or poorly reproducible, or have not been subjected to adequate statistical analysis. This review discusses the relationship to survival of clinical and pathological variables, and highlights the disadvantages of the principal staging systems that are currently in clinical use.

Tumour staging

Dukes' classification

In 1927 Lockhart-Mummery³, noting a relationship between prognosis and extension of rectal tumours, suggested a clinical classification that was later modified to include pathological data⁴. Dukes subsequently changed the criteria, developing a system for the pathological classification of rectal carcinoma⁵. Three stages were described: A, growth limited to the rectal wall; B, extension of growth to extrarectal tissues but no metastases in regional lymph nodes; and C, metastases in regional lymph nodes. Class C was later subdivided into C₁, only regional lymph nodes involved, and C₂, nodal spread to the level of the point of ligature of the blood vessels⁶. A class 'D' has crept into popular usage to indicate tumours with

phocytic infiltration was the only grade-related factor significantly related to survival.

of clinical relevance, a system of prognostic significance. Jass's classification is potentially subjective. Jass's intraobserver variation by Jass's frequently reported fair to good agreement for tumour type, lymphocytic infiltration¹⁰⁷.

The prognostic power of the extent of tumour invasion in the Dukes' classification has repeatedly been proven to be correlated with patient survival. Modifications have led to confusion, resulting in caution being required in the classification of patients with Dukes' A tumours. In the UK, the American tumour node metastasis and Australian clinicopathological systems are frequently considered too complex for routine clinical use. Meanwhile, Jass's classification may be complicated by observer variation between pathologists, and recent evidence suggests that it offers no advantage over that of Dukes. All the conventional staging systems also fail to take the skill of the surgeon into account when determining outcome. Attempts at quantifying tumour structure have not heralded the expected major advance. For instance, the expense and uncertain prognostic value of tumour DNA content assessed by flow cytometry are likely to restrict widespread use of this technique. It may soon be possible, however, to provide optimum treatment for patients based on individual tumour doubling times. Classifications using knowledge of how a small number of cells in the tumour have the ability to invade locally, enter blood vessels and metastasize would also provide important prognostic information on which treatment could be based. Until then, the ease of use and high prognostic power of Dukes' classification ensure that, after 60 years, it is still the 'gold standard' against which all other prognostic classifications in colorectal cancer should be assessed.

distant metastases. The classification was soon applied to colonic as well as to rectal tumours⁷.

Two modifications have complicated this classification. In 1949, Kirklin *et al.*⁸ subdivided Dukes' system into: A, lesion limited to the mucosa; B₁, lesion extends to, but does not penetrate, the muscularis propria; B₂, lesion penetrates through the muscularis propria; and C, lesion of either B₁ or B₂ with involvement of lymph nodes. Class C of this system was later modified by Astler and Coller⁹ into C₁, lesion limited to bowel wall with positive nodes, and C₂, lesion through all layers of bowel with positive nodes.

These changes have created more confusion than clarity, making it difficult to compare reported series¹⁰. A modified B₁ lesion corresponds to Dukes' A. Tumours classified as A, as designated by Kirklin *et al.*, and by Astler and Coller, are rare; of the 981 tumours studied by the authors of the two classifications, only nine (fewer than 1 per cent) met their criteria for stage A. In contrast, 15 per cent of tumours in the series reported by Dukes and Bussey¹¹ were classified as Dukes' A. The reported frequency of Dukes' A tumours varies from 6 per cent^{12,13} to 25 per cent¹⁴⁻¹⁷ and even 35 per cent¹⁸. Although differing referral patterns or detection of earlier lesions by colonoscopy¹⁹ may be contributory, the various interpretations of what constitutes a Dukes' A lesion account for many of these differences.

The C₁ and C₂ categories proposed by Astler and Coller⁹ are different from those described by Dukes; another source of confusion results from the use of the term 'muscularis propria'. In the colon and rectum, the muscularis propria consists of the longitudinal and circular layers of smooth muscle in the intestinal wall. Although Astler and Coller used this in their staging system, the term has subsequently been misinterpreted to mean muscularis mucosa. This has resulted in both B₁ and

to class A... *et al.* found that... and Collier A and B... level indicated by

...ins, there are deficiencies in all... analysis based on a few tissue samples... the muscularis propria, such that... quite soon are misclassified into the... es' A group. In a series of 2037 rectal... reported a crude 5-year survival rate of... patients with class A tumours, instead of the... been expected if the classification were perfect¹¹. ... histological grade of the tumour and the number of... involved nodes, which are both known to be related to survival²⁰⁻²³, are not considered in Dukes' classification. The thoroughness of the pathologist in examining for lymph nodes is also important. Blenkinsopp *et al.*²⁴, reviewing pathological assessment of the depth of tumour penetration in 2046 patients from several institutions, noted that variation between observers ranged from 5 to 30 per cent ($P < 0.001$). Differences were also noted between centres in the mean number of lymph nodes harvested per specimen ($P < 0.001$) and the proportion of cases in which no nodes were identified. Because microscopic appearances are rarely difficult to interpret, these differences are most likely to be caused by errors in the macroscopic assessment of the specimen. Such results suggest that caution is necessary when comparing the proportions of cases in the various Dukes' classes between institutions.

Despite these problems, Dukes' classification remains an extremely powerful prognostic tool. Dukes and Bussey¹¹ reported 5-year survival rates of 81.2, 64 and 27.4 per cent for patients with A, B and C tumours, respectively, figures comparable to those of most modern series. Studies employing univariate analysis^{12,25-29} have repeatedly emphasized the prognostic importance of tumour staging in colorectal cancer. Similarly, major series employing multivariate analysis have identified tumour stage as the primary determinant of prognosis in colorectal cancer^{15,17,22,30-33}. The only improvement required on Dukes' assessment of the degree of tumour penetration may be the use of Astler and Collier stages C₁ and C₂. Multivariate analysis has revealed this to be superior to a single Dukes' C class, and to be independent of the number and site of nodal metastases and the degree of tumour differentiation²⁰.

In summary, the deficiency of Dukes' classification is that it fails to take clinical factors and the number of involved nodes into account. Modifications have resulted only in confusion over the interpretation of the various classes, particularly A. In spite of these problems, the prognostic significance and comparative ease of Dukes' classification ensure that it remains the 'gold standard' against which all other prognostic variables in colorectal cancer should be tested.

Clinicopathological staging

The tumour node metastasis system

In an attempt to overcome the problems of Dukes' classification a clinicopathological system was proposed³⁴. This consisted of grading the extent of the primary tumour (T), the condition of regional lymph nodes (N) and the presence or absence of distant metastases (M). The Union Internacional Contra la Cancrum, however, agreed that the extent of colonic carcinoma could not be fully assessed clinically at the time of surgery. The American Joint Committee on Cancer therefore developed a series of prefixes for the TNM classification to relate to the extent of the disease at given sites and times³⁵⁻³⁹. These are: cTNM, clinical diagnostic staging; sTNM, surgical evaluative staging; pTNM, postsurgical pathological staging; rTNM, retreatment staging (e.g. at second laparotomy); and aTNM, autopsy staging.

This American TNM classification was considered by many

to be too complex for routine use. In Australia a separate clinicopathological system was developed. This employed an A, B, C, D grading but combined clinical information, curative or palliative operation status, and a pathological subdivision of Dukes' classes before a final grade was ascribed⁴⁰⁻⁴⁶. In Spain a further system, based on a subclassification of Dukes' 'D' tumours, was developed⁴⁷. This international variation in the surgical, clinical and pathological classifications was addressed in 1987 with the adoption of identical criteria between countries^{48,49}; guidelines for an internationally agreed staging system were proposed^{50,51}. Despite attempts to produce a standardized clinicopathological classification⁵², the TNM system is complex relative to Dukes' classification. For instance, subdividing patients into T₁N₀M₀ and T₂N₀M₀ does not significantly improve the prediction of survival over a simple Dukes' A classification²⁰. Consequently, the TNM system has not become widely accepted in the UK.

Other clinicopathological variables

In an attempt to improve on both Dukes' and the TNM classifications, several studies have assessed the prognostic significance of numerous clinical and pathological variables. These include tumour size⁵³, lymphatic invasion⁵⁴⁻⁵⁶, mucinous tumours⁵⁷, laminin⁵⁸, involvement of the lateral resection margin^{30,59,60}, silver-binding nucleolar organizing regions⁶¹⁻⁶³, lymphocytic and vascular invasion in the individual Dukes' classes⁶⁴, biochemical markers⁶⁵, blood-group antigens⁶⁶⁻⁶⁹, carcinoembryonic antigen⁷⁰⁻⁷² and CA 19-9⁷³⁻⁷⁷. Despite suggestions that some of these variables may be related to survival on univariate or multivariate analysis, none consistently improves on the prognostic value of Dukes' classification in a regression analysis model. Three clinicopathological variables, however, are often related to survival and warrant further discussion. These are patient age, histological grade and venous invasion.

Patient age. The most important clinical variable appears to be patient age. Whether older or younger patients have the poorer prognosis is, however, unclear. Several studies have reported that increasing age is associated with a poorer prognosis^{15,17,78-80}. This appears to be independent of the fact that older patients are more likely to die from their operation⁸¹ or concomitant disease⁸² than are younger patients. Nevertheless, recent reports have suggested that age itself should not be a determinant when considering operation in patients with colorectal cancer⁸³⁻⁸⁵. In contrast, some authors have noted a particularly poor prognosis in those aged <40 years at presentation. Adam *et al.*⁸⁶ found that if elderly patients survived their operation they had a better prognosis than did younger patients. Gill and Morris¹² reported a significantly shorter survival in patients aged <35 years. Recio and Bussey⁸⁷ found that 45.6 per cent of patients presenting with rectal cancer before the age of 30 died in the first year, the crude 5-year survival rate being only 19.5 per cent. They stated, however, that the 'accepted gloomy prognosis for young patients with rectal cancer is confirmed only for those with lymphatic metastases; for those without them, the outlook is hopeful'. A similarly optimistic outlook was reported by Umpleby and Williamson⁸⁸, who noted that the 5-year survival rate of patients aged <40 years was comparable to that of patients of all ages. This is possibly the result of any unfavourable pathological features being balanced by improved survival after emergency operation. Similar conclusions were drawn by Okuno *et al.*⁸⁹, and Smith and Butler⁹⁰ commented that late diagnosis may be the reason for the poor prognosis in some young patients. Thus, although the evidence concerning young patients as a whole is conflicting, it appears that if they are diagnosed at an early stage the prognosis is no worse than that for older patients.

Histological grading. In 1928 Rankin and Broders⁹¹ considered the degree of cellular differentiation in rectal

carcinoma. The overall mortality rate for grade I tumours (at least 75 per cent of cells differentiated) was 44 per cent, compared with 86 per cent for grade IV tumours (fewer than 25 per cent of cells differentiated), indicating a relationship between differentiation and survival in colorectal cancer.

Grading was simplified by Grinnell⁹² into three categories: well, moderately, and poorly differentiated. He identified the histological features of grading, including those subsequently investigated by Jass *et al.*^{22,57}. These included whether the tumour was predominantly papillary, tubular or mucinous in type, the complexity of any identified tubules, the relationship of nuclei to the basement membrane (nuclear polarity) and the invasive pattern of the tumour. The degree of differentiation was then decided according to the degree of tubular arrangement, nuclear polarity, invasive tendency and frequency of mitosis. Grinnell also noted that variations in differentiation occurred in the same cancer specimen; consequently, several areas should be examined, with the most anaplastic being taken as the grade for the tumour as a whole⁹². It is now recognized that histological grade is consistent throughout the specimen in only 28 per cent of tumours^{93,94}.

This leads to potential interobserver and intraobserver variation in grading among pathologists. Grading by the same observer is reasonably reproducible, whereas grading of the same specimens by different pathologists is more variable^{17,57,94,95}. The subjective nature of the diagnostic criteria used in grading results in observers showing wide variations in bias towards either end of the differentiation spectrum, as well as in their willingness to depart from the middle ground and allocate extreme grades⁹⁵.

Despite these problems, studies employing multivariate analysis have repeatedly highlighted the importance of histological grading as an independent prognostic variable in colorectal cancer^{17,31-33,57,94}. Stipulating only two grades (poor and not poor differentiation) may overcome the difficulties of tumour grading and ensure its role as a prognostic factor in the future⁶⁰.

Venous invasion. The incidence of invasion of local veins by rectal carcinoma varies from 11 to 72 per cent, with 5-year survival rates of up to 47 per cent having been reported if invasion is present, compared with 73 per cent when it is not^{11,96-101}. Talbot *et al.*¹⁰¹ have emphasized the importance of classifying venous invasion into extramural *versus* intramural, and thick-walled as opposed to thin-walled veins, thick-walled extramural vein involvement carrying the poorest prognosis. Venous spread was related to local spread (Dukes' classification) and lymph node metastasis, and appeared to have an independent influence on prognosis^{101,102}. Recent studies, while supporting the role of venous invasion in survival in colorectal cancer, have shown considerable overlap in survival rates between patients with and without venous invasion^{103,104}. Therefore, although there is a tendency for venous invasion to be associated with distant metastasis and a lower 5-year survival rate, the prognostic significance of this finding remains to be established.

Pathological staging

Jass's classification

It became apparent that Dukes' classification, although extremely helpful and simple to use, failed to employ potentially important clinicopathological variables, while the TNM system, containing some of these variables, was too complex for routine use. The advent of multivariate survival analysis allowed Jass and co-workers⁵⁷ to develop a system based on tumour stage and a series of pathological variables related to histological grade. This classification was claimed to be superior to that of Dukes^{22,57,105,106}. Although all of the grade-related variables investigated by Jass *et al.*⁵⁷ correlated with survival on univariate analysis, only three remained important after Cox's regression analysis⁵⁷. After correction for Dukes' class,

the degree of lymphocytic infiltration was the only variable that remained significant.

However, to be useful, a classification must be reproducible as well as valid. Jass's classification relies on the pathologist's subjective assessment, which is then translated into verbal categories and is therefore subjective. Jass and colleagues⁵⁷ initially assessed the reproducibility of their classification by having one specialist pathologist and subsequently two assess the same slides. They achieved excellent levels of interobserver agreement for differentiation, growth pattern and lymphocytic infiltration. These assessments were performed by specialists from a centre dealing almost entirely with colorectal cancer. Reports using non-specialist general pathologists, which may be more relevant to the majority of pathology departments nationwide, have implied that observer consistency regarding many of the components of Jass's classification is poor^{17,108}. In particular, the intraobserver and interobserver variation of lymphocytic infiltration in some series was little better than chance^{17,108}. This is significant, as lymphocytic infiltration may be the only variable of Jass's classification that is consistently related to survival¹⁰⁹. These findings highlight the subjective nature of the components of Jass's classification and cast doubt on its clinical significance. Indeed, Secco *et al.* found no significant difference in survival between Jass's grades II and III, even though these accounted for the majority of patients in their study¹⁰⁹.

Reports employing both Dukes' and Jass's classifications have suggested that the former was more significantly related to survival on multivariate analysis^{17,20}. Fisher *et al.*²⁰ compared the prognostic values of the Dukes and Jass systems in 722 patients with rectal cancer. The Jass system allowed for only two major prognostic groups, whereas five were noted by Dukes' method. Fisher *et al.* concluded that the more objective nature of Dukes' classification warranted its continued use for prognosis and therapeutic decisions for patients with rectal cancer in preference to Jass's system. The subjective nature and complexity of Jass's classification relative to that of Dukes support this conclusion.

Quantitative pathology

The knowledge that cancer cells are characterized by enlarged nuclei and abnormal DNA stem lines or ploidy led to investigation of whether techniques that can identify such changes may improve the deficiencies in the present pathological classifications. Considerable interest has focused on the relative DNA content (ploidy) of tumours, as assessed principally by flow cytometry. The prognostic value of DNA ploidy assessed by this technique is, however, uncertain. Studies on both fresh and paraffin-embedded material consistently show a trend for tumours with near-normal DNA content (diploid) to carry a better prognosis than those with abnormal (aneuploid) DNA composition. However, the reported significance of ploidy as an independent prognostic variable in colorectal cancer varies considerably.

Several reports on both small¹¹⁰⁻¹¹⁴ and large^{23,115-121} numbers of patients have suggested that DNA content is of independent prognostic significance. Nevertheless, studies employing multivariate analysis have confirmed the prognostic importance of Dukes' classification to be much greater than that of DNA ploidy^{23,32,33}. Others have found that ploidy is significantly related to survival only in patients with a better prognosis according to Dukes' classification^{23,118,122}. Different reports have suggested that DNA ploidy is not significantly related to survival in any group of patients^{15,17,123,124}.

These flow cytometric studies measured the DNA status of both normal and tumour cells comprising the specimen. DNA densitometry, which can assess the ploidy status of tumour cells alone, may allow a more accurate analysis of the DNA status of a tumour. The few studies using this technique have suggested that, although diploidy confers a better survival advantage than aneuploidy, DNA ploidy status is not of independent prognostic significance in colorectal cancer^{17,125,126}. Indeed, reports on

both flow cytometry^{17,127} and densitometry¹²⁸ have suggested that any significant relationship between ploidy and survival varies; analysis disappears on subsequent multivariate analysis.

It appears that the assessment of nuclear DNA by flow cytometry or densitometry, as well as the assessment of nuclear shape by morphometric image analysis¹⁷, is too crude a measure of nuclear abnormality to be of prognostic significance in colorectal cancer. The prognostic value of such factors, compared with that of Dukes' classification, seems minimal.

Conclusion

Attempts at improving the survival of patients with colorectal cancer have focused on preventative measures as well as treatment of established disease. There has been much interest in the aetiology of the disease, leading to theories on the importance of dietary factors¹²⁹⁻¹³¹, pathological conditions¹³²⁻¹³⁵, family history¹³⁶ and genetics¹³⁷⁻¹³⁹. However, it will be many years before changes in these factors will reduce the incidence of colorectal cancer.

Surgery remains the mainstay of treatment, but the skill of the surgeon is not taken into account in any of the present staging systems. Also, despite considerable advances in surgical techniques, the outlook for affected patients has changed little over the past 50 years. Future improvements may lie in the use of increasingly effective forms of adjuvant therapy¹⁴⁰. However, none of these has so far consistently been shown statistically to improve the survival of all patients with colorectal cancer. At present, many clinicians restrict adjuvant therapy to those with a dismal outlook. The best chance of improving survival in patients with advanced colorectal cancer is to select those who will benefit most from such therapy. This is presently not possible, although the estimation of tumour doubling times by dual parameter flow cytometry may prove helpful^{141,142}. Tumour classifications based on knowledge of how a small number of cells in the tumour have the ability to invade locally, enter blood vessels and metastasize would also provide important prognostic information on which treatment might be based. Until such advances are established, clinicians will have to rely on the present prognostic classifications¹⁰⁵. As this review demonstrates, none of these is perfect in the routine clinical setting; however, Dukes' classification still remains the single best predictor of survival in colorectal cancer after almost 60 years.

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Nutrition and malignant disease: implications for surgical practice

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Malignant disease is often associated with weight loss and malnutrition. Nutritional support is frequently provided to patients with cancer in an attempt to improve nutritional status and reverse weight loss, with the aim of reducing morbidity and mortality rates. This review evaluates the effect of supplemental nutrition on morbidity and mortality in patients with malignancy undergoing treatment with surgery, chemotherapy or radiotherapy. It also assesses the effect nutritional supplementation has on host defence mechanisms and how nutrients affect tumour cell growth. The evidence suggests that perioperative nutritional support, if given for at least 10 days, reduces morbidity and mortality in patients with biochemical evidence of severe malnutrition, manifest as a low serum albumin concentration and excessive weight loss. In contrast, there is no evidence that parenteral nutritional support benefits patients undergoing chemotherapy or radiotherapy, in terms of either an increased tumour response rate or prolongation of survival. Current research on malignant disease is highlighting the role of specific nutrients (amino acids, essential fatty acids and polyribonucleotides) as key regulators of both anticancer host defence mechanisms and the control of nitrogen metabolism and tumour growth. Arginine, essential fatty acids and ribonucleotides have all been demonstrated to stimulate antitumour host defence mechanisms and some also modulate tumour cell metabolism. Dietary manipulation offers exciting possibilities for the innovative management of malignant disease.

Malignant disease is frequently accompanied by weight loss and malnutrition, which in its most severe form is referred to as 'cancer cachexia' and characterized by anorexia, skeletal muscle atrophy, tissue wasting and organ dysfunction¹. A detailed study of malignant disease revealed that 28 per cent of patients with colorectal carcinoma and 14 per cent of those with breast cancer had lost > 5 per cent of their body-weight in the 6 months before diagnosis². This weight loss and malnutrition have prognostic significance. Patients without weight loss survive longer than those who have lost > 5 per cent of their body-weight², and reduction in some of the indices of nutritional status (serum albumin, creatinine:height ratio, triceps skinfold thickness) are associated with an increased mortality rate in patients with cancer³. Furthermore, malnourished patients undergoing cancer surgery have high complication rates^{3,4}. Supplemental nutrition, therefore, has been provided in an attempt to improve nutritional status. Approximately one-third of patients receiving parenteral nutrition have cancer⁵, but the indications for and possible benefits of such therapy are, at present, contentious. This review addresses the following questions: What is the effect of supplemental nutrition on the morbidity and mortality of patients with cancer undergoing treatment by surgery, chemotherapy or radiotherapy? What beneficial effects, if any, does supplemental nutrition have on protein metabolism (muscle wasting) and host defence mechanisms? Do nutritional supplements or specific nutrients modulate tumour cell growth and thereby have a pharmacological role?

Effect of nutritional support on morbidity and mortality

Perioperative nutritional support

Studies have been undertaken to determine whether patients

with malignant disease achieve a reduction in morbidity and mortality rates from nutritional support given in the perioperative period. Such support, administered by the oral or parenteral route, has yielded variable results. The first randomized trial to address this question was reported in 1977 by Holter and Fischer⁶. The study group, 30 patients with upper gastrointestinal malignancy who had lost > 4.5 kg in the 3-month period before surgery, received 80 g protein and 2000 kcal/day intravenously, starting 72 h before surgery and continuing for 10 days afterwards. The control group, 26 patients with a similar weight loss, did not receive nutritional support. Mortality was the same in the two groups (two patients died in each), but major postoperative complications (prolonged ileus, intestinal obstruction, fistulation, wound dehiscence, anastomotic leakage) occurred more frequently in the control group. Intravenous nutrition reduced (but not significantly) the rate of major complications from 19 to 13 per cent. This study has been criticized for its small number of patients and the inability of 72 h of preoperative nutritional support to alter nutritional state significantly.

Moghissi *et al.*⁷ also carried out a randomized study in patients with oesophageal carcinoma undergoing thoracotomy. Fifteen patients were entered and ten were randomized to receive approximately 35 kcal per kg body-weight and 0.2 g nitrogen per kg body-weight daily for 5-7 days before and 6-7 days after surgery. Five patients in the control group were given only dextrose-saline (6 kcal per kg body-weight daily) over the same period. Patients in both groups had similar weight loss before operation (1.8-5.9 kg). Increased morbidity - impaired wound healing - was documented in four of the five patients in the control group. The first study to show significant beneficial effects was reported in 1979 by Heatley *et al.*⁸. Seventy-four patients with oesophageal or gastric cancer were

Table 1 Studies of nutritional support in patients with gastrointestinal malignancy

Reference	Type of patient	No. of patients	Nutritional support	Malignancy	Improvement with nutritional support	Mortality rate
12	Preoperative	23	TPN <i>versus</i> low-calorie diet for 8 days	Stomach	Increased serum albumin and responses to mitogens	No difference
6	Perioperative	56	TPN <i>versus</i> standard oral diet for 3 days before and 10 days after surgery	Gastrointestinal tract	Increased serum albumin	No difference
7	Perioperative	15	TPN <i>versus</i> standard oral diet for 5–6 days before and 6–7 days after surgery	Oesophagus	Improved nitrogen balance	No difference
8	Preoperative	74	TPN <i>versus</i> standard oral diet for 7–10 days	Stomach and oesophagus	Reduced wound infection	No difference
10	Preoperative	125	TPN <i>versus</i> standard oral diet for 10 days	Gastrointestinal tract	Reduced major complications	3 per cent in TPN group, 11 per cent in controls
13	Perioperative	21	TPN <i>versus</i> standard oral diet for 5 days before and 8 days after surgery	Gastrointestinal tract	Increased weight	No difference
14	Preoperative	19	TPN <i>versus</i> gastrostomy fed for 4 weeks	Oesophagus	Increased weight	No difference
15	Perioperative	459*	TPN <i>versus</i> oral diet for 7–15 days before and 3 days after surgery	Thoracic and abdominal*	Reduced major complications in severely malnourished subgroup	No difference

TPN, total parenteral nutrition; *66 per cent of the 459 patients had malignant disease, but this subgroup was not analysed separately

randomized to receive either intensive oral feeding ($n = 38$) or combined oral and intravenous feeding ($n = 36$) for 10 days before surgery. A significant reduction in wound infection in the intravenously fed group was recorded, confined to a subgroup of patients with a serum albumin level of <35 g/l on admission. The authors questioned whether the costs and side-effects of total parenteral nutrition (TPN) outweighed the benefits of a decrease in wound infection. Mullen *et al.*⁹ compared the effect of 10 days of preoperative TPN ($n = 50$) with that of a standard oral hospital diet ($n = 95$) in patients undergoing surgery for intra-abdominal malignancy. The groups were matched for nutritional status and assessed by serum albumin <35 g/l, negative responses to skin antigens, and weight loss >5 kg in the preceding 12 months. Although this study demonstrated a significant decrease in major complications and mortality in the group receiving TPN, the intake of those receiving oral nutrition was not controlled. Similar results were reported by Muller *et al.*¹⁰, who demonstrated a significant reduction in mortality rate and anastomotic breakdown after operation in 66 patients with gastric and oesophageal carcinoma fed parenterally for 10 days before operation, compared with a control group of 59 patients not receiving supplementation. This last study is frequently cited in support of perioperative nutrition. It is worth noting, however, that when the surgeons began stapling their anastomoses, anastomotic leakage – which was the major cause of the mortality and morbidity – was reduced substantially, whether or not patients received nutritional supplementation¹¹.

Clinical benefit from supplemental nutrition has not been a consistent finding and other studies (Table 1) have failed to show significant benefit from nutritional support. These have, however, been criticized because of the small numbers of patients, lack of randomization, use of unsuitable control groups, differences in nutritional status before surgery and inadequate quantity or duration of nutrition. Detsky *et al.*¹⁶ carried out a meta-analysis of trials of perioperative nutritional support and, despite the limitations of many of the studies, found that nutritional supplementation reduced the morbidity rate by 21 per cent and the mortality rate by 32 per cent after major surgery, although it was not possible to identify clearly which particular patients would benefit. There was, in addition, appreciable morbidity associated with TPN; major iatrogenic complications were documented in 7 per cent of patients.

In the absence of substantive and carefully documented data it has been difficult to make absolute recommendations, but the American Society of Parenteral and Enteral Nutrition recommended that nutritional support be provided for patients who are: severely malnourished before surgery; well nourished before surgery, but have complications that result in 10–14 days of inadequate nutritional intake; or well nourished before surgery, but expected to have inadequate intake for 10–14 days because of the nature of their surgery¹⁷. These guidelines unfortunately failed to define either 'malnutrition' or how nutritional status should be assessed.

A major difficulty in evaluating such studies is the inadequacy of the evaluation of nutritional status. This has been assessed by using anthropometric measurements (weight loss, body-mass index, skinfold thickness), biochemical data (levels of serum albumin, retinol binding protein, prealbumin), immunological analyses (lymphocyte counts, delayed-type hypersensitivity reactions) and muscle function tests (grip strengths). In addition, combinations of these measurements have been used to calculate prognostic nutritional indices¹⁸, which are determined largely by plasma protein levels. These have not gained widespread acceptance in clinical practice because of their lack of specificity in identifying the malnourished patient at risk of complications. Furthermore, it has been shown that a clinical assessment based on the patient's history and physical examination, when evaluated by a trained clinician, is at least as good as laboratory measurements in identifying the malnourished patient¹⁹. In a review of published data, Hill²⁰ concluded that a careful dietary history and physical examination, weight loss >10 per cent, clinical evidence of respiratory and limb muscle weakness, and a plasma albumin level <32 g/l 'should alert the clinician to the possibility of increased risk of nutrition-associated complications' and thus identify individuals who may benefit from nutritional supplementation.

Some of the limitations of these previous studies such as the small number of patients, inclusion of patients who were not malnourished, and poor study design have been addressed in the Veterans' Affairs Total Parenteral Nutrition Cooperative Study¹⁵. A major multicentre randomized study was undertaken that evaluated the efficacy of perioperative parenteral nutrition in patients undergoing abdominal or thoracic surgery, with 66 per cent of these having malignant

Table 2 Studies of nutritional support in patients receiving radiotherapy for malignant disease

Reference	Nutritional support	No. of patients	Malignancy	Improvement with nutritional support	Group had a significantly better outcome with nutritional support
25	TPN <i>versus</i> standard oral diet	81	Ovarian and gastrointestinal tract	Fewer side-effects with therapy, increased weight	No difference
26	TPN <i>versus</i> standard oral diet	81	Ovarian	Less malnutrition	No difference
27	Oral supplements <i>versus</i> roughage	47	Bladder and prostate	None	No difference
28	TPN <i>versus</i> standard oral diet and supplements	20	Abdominal and pelvic	Increased body-weight and increased serum transferrin	No difference
29	TPN <i>versus</i> standard oral diet	32	Genitourinary tract	Increased weight	No difference
30	Standard diet <i>versus</i> supplementation with elemental diet	30	Gastrointestinal tract	None	No difference

TPN, total parenteral nutrition

disease. In all, 459 patients were randomized to receive either TPN supplementation or an oral diet for 7–15 days before and 3 days after surgery (the mean daily calorie intake in the TPN group was 2944 kcal and in the oral group 1280 kcal, with a calorie:nitrogen ratio of 150 kcal per g nitrogen. Results from this study showed that there was no overall difference in morbidity and mortality rates between the patients receiving supplemental TPN and those taking an oral diet. Furthermore, the incidence of infectious complications and the length of hospital stay were greater in the TPN group. However, subgroup analysis revealed that if patients were 'severely malnourished' (defined by subjective global assessment or a nutrition risk index based on serum albumin levels and weight loss²¹) they benefited from TPN supplementation. Such patients had a reduced incidence of major complications such as anastomotic leakage, bronchopleural fistula and organ dysfunction compared with the control group of severely malnourished patients.

In summary, these studies indicate that patients should be evaluated in terms of their nutritional status and that an assessment of the degree of malnutrition should be made. If patients are not severely malnourished then there is no evidence to support routine use of perioperative parenteral nutrition, but those that are severely malnourished will probably benefit from nutritional supplementation, although the evidence for this remains inconclusive²².

Nutritional support and chemotherapy

Initial studies in animals with tumours investigated the effect of nutritional support in association with chemotherapy. They showed that nutritional supplementation resulted in improved nitrogen balance and nutritional status, reduction in the toxicity of chemotherapy and enhanced survival²³. During intensive chemotherapy or radiotherapy, oral intake is often decreased because of anorexia, aversion to food, alteration in taste, diarrhoea and malabsorption. Parenteral nutrition is often given to patients undergoing chemotherapy with the intention of improving or maintaining their nutritional status and thereby the clinical outcome.

The effect of parenteral nutrition in patients undergoing chemotherapy has been extensively investigated in terms of survival, tumour response and toxicity of treatment. These studies were reviewed by Koretz¹¹ who found a wide variation in their results. He concluded that parenteral nutrition did not alleviate the toxicity induced by chemotherapy, failed to alter the response of the tumour to therapy, and did not improve survival. A more extensive analysis of published data on the effect of nutritional support in patients undergoing chemotherapy was carried out by McGeer *et al.*²⁴. This revealed that patients given nutritional support were less likely to survive or achieve a therapeutic response than those not receiving supplementation. Furthermore, patients receiving nutritional support had a risk of infection four times higher than that of

control patients. Included in this analysis, however, were studies in which the nutritionally supported group had a higher proportion of patients with more advanced malignant disease and metastasis compared with the control group; these patients consequently had a higher mortality rate, biasing the analysis. Nevertheless, McGeer *et al.*²⁴ concluded from their meta-analysis that, although there might be subgroups (e.g. severely malnourished patients) who might benefit from supplemental nutrition, nutritional support in patients receiving chemotherapy was, overall, associated with 'net harm and no conditions could be clearly defined in which such treatment appeared to be of benefit'. This is contrary to widely held beliefs and to the current practice of many oncologists.

Nutritional support and radiotherapy

Studies of nutritional support in patients with malignancy undergoing radiotherapy are documented in Table 2. Solassol and colleagues^{25,26} randomized patients with stage III and IV ovarian cancer to receive TPN supplementation ($n = 42$) or a standard oral diet ($n = 39$) while undergoing radiotherapy. Unfortunately, the nutritional status and degree of weight loss were not well defined, and the length of treatment and duration of nutritional support inadequately documented. Patients receiving TPN had a reduction in episodes of abdominal pain, diarrhoea and vomiting but survival was not affected. Subsequently, Brown *et al.*²⁷ randomized patients with a variety of cancers (mainly of the bladder and prostate) who were undergoing radiotherapy to receive either a low-roughage or an elemental diet. Again, the nutritional status and degree of weight loss were unknown, and the length of nutritional supplementation and treatment not stated. The only index of morbidity studied was stool frequency and this was not different between the two groups; no comment was made on overall survival. There has been no convincing evidence published showing benefit from nutritional support during radiotherapy (Table 2). In the absence of significant benefit, and taking into account the problems encountered with previous studies, no recommendations can be made for the use of nutritional supplementation in patients undergoing radiotherapy. Further, well designed and carefully controlled studies will be needed to determine which patient groups may derive clinical benefit.

Administration of nutritional support: the enteral *versus* the parenteral route

Many studies evaluating the effects of nutritional support that have used intravenous feeding have documented morbidity, primarily from catheter-related sepsis. It has also become clear that nutrition given enterally is as effective as that administered via the parenteral route. Both before and after operation an enteral diet is as effective as parenteral nutrition in maintaining nutritional status^{31–33}.

...the relationship of the nutritional support to the intestinal tract function and structural integrity. One of the primary functions of the small intestine is digestion and absorption of nutrients. In the absence of enteral feeding, even in the presence of adequate parenteral nutrition, pathological changes take place in the small intestinal mucosa, including a reduction in height of the villi and a decrease in activity of brush border enzymes³⁴. Another function of the intestinal mucosa is the prevention of bacterial translocation from the lumen into the systemic circulation. Enteral nutrition is better than TPN in maintaining intestinal function and structure³⁵. The amino acid glutamine, which is a primary fuel for enterocytes³⁶, is of particular importance in maintaining mucosal metabolism, structure and function³⁷. Studies on animals have found that increasing the glutamine content of enteral nutrition resulted in a decrease in bacterial translocation³⁸ and, in a radiation enteritis model, increased the recovery of the bowel from radiation and reduced treatment-related morbidity and mortality rates³⁹. Further studies in humans are required to clarify this potentially beneficial effect of glutamine supplementation.

Provision of nutritional support by an enteral diet in the presence of a functioning gastrointestinal tract is as effective as the intravenous route in maintaining a satisfactory nutritional state, simpler to administer, cost effective, and reduces the treatment-related morbidity relative to parenteral nutrition⁴⁰.

Effects of nutrition on protein metabolism and host defence mechanisms

Protein metabolism

A major component of weight loss in malignancy is loss of protein from skeletal muscle, which is manifested clinically by muscle wasting. Proteins are continually being synthesized and degraded, and in the healthy adult these processes cancel out so that a state of nitrogen balance exists. In patients with cancer a negative nitrogen balance is present in 30–100 per cent of cases⁴¹. The effect of supplemental nutrition has been assessed by measuring alterations in nitrogen balance, serum proteins and body-weight. Patients with a variety of malignancies receiving different supplemental nutritional regimens have been studied, but no consistent beneficial effect has been documented^{42–47}. Nutritional supplementation was shown in some studies to increase weight, effect a positive nitrogen balance, increase levels of serum proteins, and improve responses to skin antigens^{42–47}. There are, however, difficulties in interpreting the results of these studies because weight gain may not be due to an increase in protein, as body composition analyses have demonstrated a differential increase in fat and water, rather than protein alone⁴⁸. Furthermore, nitrogen balance studies provide only a limited amount of information, because nitrogen loss may occur by a number of pathophysiological mechanisms such as a decrease in the rate of protein synthesis, an increase in the rate of protein breakdown, or various combinations of alterations in these two processes.

Studies of whole-body protein turnover measuring rates of whole-body synthesis and breakdown in patients with cancer receiving nutritional support have been undertaken but with conflicting results. Nutritional support has been variously reported to stimulate whole-body protein metabolism⁴⁹, to have no effect⁵⁰, or to inhibit synthesis in combination with a greater reduction in breakdown^{45,46}. These investigations contained small numbers of patients and it is unclear whether these were febrile at the time of measurement; pyrexia can increase protein turnover rates⁵¹. The reasons for the discrepancies are not clear, but might be related to different types of tumour, the presence of metastasis, the nutritional status of the patient, varying experimental protocols, or differences in methods of measuring protein turnover⁵². On balance, however, the above results suggest either an increase in protein accumulation or no effect from supplemental feeding;

the clinical relevance of these metabolic changes is, however, unclear.

Host defence mechanisms

Malnutrition has long been known to impair both humoral and cell-mediated immune responses, and nutritional repletion to reverse some of these deficiencies^{53,54}. Furthermore, recent studies have found that severe malnutrition results in an alteration in the T cell subsets, with a reduction in the circulating levels of both T-helper cells (CD4) and T-suppressor/cytotoxic (CD8) lymphocytes⁵⁵. Patients with cancer also have impaired immune responses which are induced by the malignant process⁵⁶; the effect of nutritional support on the defence mechanisms of such patients requires further investigation.

Several studies have evaluated the effect of nutritional support on immune function in patients with a range of cancers; results have varied, making it difficult to draw general or specific conclusions. Two particular papers illustrate these difficulties. Yamada *et al.*¹² studied patients with advanced gastric cancer undergoing surgery and compared the effect of 18 days of TPN after operation in 11 patients with a control group of 12 receiving low-calorie fluid only. The group receiving TPN had significantly enhanced lymphocyte counts, enhanced delayed-type hypersensitivity reactions and an increased percentage of T cells in the circulating lymphocyte compartment. In contrast, Monson *et al.*⁵⁷ studied the effect of 7 days of TPN in patients with colorectal and gastric cancer, before and after TPN (given before surgery was carried out). The TPN, however, contained Intralipid (Kabi Pharmacia, Milton Keynes, UK), which has been suggested by some investigators to be immunosuppressive⁵⁸. Although the response of blood lymphocytes to stimulation with mitogens and production of interleukin 2 *in vitro* was enhanced, there was a significant reduction in natural killer (NK) cell and lymphokine-activated killer (LAK) cell activity⁵⁹. The authors suggested that inhibition of natural cytotoxicity might contribute to the rapid progression of malignancy previously observed in some patients with cancer receiving nutritional supplementation.

Many factors modulate host defence mechanisms and the effect of nutrition is difficult to evaluate in patients with cancer. Suppression of immune reactivity is influenced by the tumour volume and the biological characteristics of the malignant process, as well as by the variable degree of malnutrition. Recent studies, however, have focused on certain specific dietary constituents that appear to have an important role in modulating aspects of immune responses: in particular, their effects on NK and LAK cell cytotoxicities, which are believed to play a crucial role in the destruction of malignant cells, especially those initiating metastases⁵⁶. Substances that have attracted particular interest are the amino acid arginine, polyunsaturated fatty acids (PUFAs) and nucleotides.

Arginine. Arginine is obtained from dietary sources and endogenous synthesis by the urea cycle in the liver. It is essential for normal tissue growth and development, and has important effects on host defence mechanisms. In animals it has a thymotropic effect⁵⁹; excess arginine has been shown to increase phagocytic activity in macrophages and enhance production⁶⁰ of the cytokine interleukin 2.

A randomized controlled trial was carried out by Daly *et al.*⁶¹, who supplemented enteral feeding of 16 patients undergoing major surgery for cancer with arginine (25 g/day) for 7 days after surgery, and compared results with those from a control group of 14 patients receiving supplementation with an isocaloric amount of glycine. The arginine-supplemented group showed an enhanced lymphocyte response to mitogen stimulation *in vitro* and an increased percentage of circulating T-helper lymphocytes, suggesting that arginine was able to reverse the inhibition of cell-mediated immunity induced by surgical trauma. Park *et al.* have recently shown that 30 g arginine, given orally for 3 days, increased the number of

circulating NK and LAK cells and enhanced substantially the NK and LAK cell cytotoxicities in healthy volunteers⁶² and women with breast cancer⁶³.

Fatty acids. The essential fatty acids (EFAs) cannot be synthesized by the human body and are obtained from the diet. The parent fatty acids are linoleic acid and α -linolenic acid, which are abundant in food. Once absorbed, they undergo a series of reactions, an important step being the conversion of linoleic acid to γ -linolenic acid (GLA) by the $\Delta 6$ -desaturase enzyme complex. Further enzyme-induced structural changes produce longer chain fatty acids which can be converted into prostaglandins or leukotrienes or incorporated into cell membranes.

PUFAs are also believed to play a role in the regulation of immune mechanisms, by altering lymphocyte membrane composition after stimulation with antigens or mitogens, and by altering the fatty acid content of lymphocytes by changes in dietary fats⁶⁴. Alterations in membrane lipid composition can lead to changes in enzyme activities, membrane fluidity and receptor expression, and thus function, of lymphocytes⁶⁴. Most experimental studies have evaluated the role of PUFAs in animal models of sepsis and have documented beneficial effects on the immune system⁶⁵. PUFAs selectively enhance the cytotoxicity of T cells and macrophages, which have an antitumour activity. The role of PUFAs, if any, in modulating NK and LAK cells is poorly understood and requires further study.

Nucleotides. Nucleotides (composed of a base, a pentose sugar and phosphate groups) are not only essential components of DNA and RNA but are also important regulators of the immune response. Animal studies^{66,67} have shown that dietary nucleotide restriction results in an impairment of cellular immunity, with reduced responses of lymphocytes to T cell mitogens, reduced delayed-type hypersensitivity reactions, and decreased production of interleukin 2. In protein-restricted animals with impaired immune responses, immunological competence was restored by providing supplementation with RNA⁶⁸. Synthetic double-stranded polyribonucleotides (e.g. polyadenylic-polyuridylic acids) are recognized biological response modifiers, enhancing release of γ -interferon and stimulating NK cell activity^{69,70}. They have been used as adjuvants in patients with solid tumours (e.g. of the breast and stomach)^{71,72}. A randomized trial comparing polyadenylic-polyuridylic acid with placebo in patients with operable breast cancer demonstrated a significantly enhanced survival in postmenopausal women⁷². This beneficial effect was most marked in those with three or fewer axillary nodes involved. Further studies are currently evaluating the use of this polyribonucleotide in patients with malignant disease.

Modulation of tumour growth by exogenous nutrients

A major concern has always been that nutritional supplementation could stimulate tumour growth. Studies on animals have addressed this question by measuring tumour characteristics such as volume, weight and mitotic activity, as well as DNA and RNA concentrations and protein synthesis, using these variables as indices of tumour growth. Some investigators have reported tumour growth to be significantly increased by nutritional support, and in some cases the stimulation of growth was greater in the tumour than in the host tissues⁷³⁻⁷⁶. These experiments may be criticized in that they utilized rapidly growing transplanted tumours that result in a large mass relative to the host animal and do not reflect the situation in humans. Not all studies have confirmed these findings; Kishi *et al.*⁷⁷ found no significant stimulation of protein synthesis in rat carcinosarcomas after 7 days of nutritional support. A trend towards stimulation of protein synthesis was demonstrated but the numbers of animals in the experimental groups were small and the difference not significant. Similarly, King *et al.*⁷⁸ failed

to demonstrate an increase in protein synthesis in tumour support but in this study the control group received a greater protein intake than that receiving the experimental diet. Data from animal studies, therefore, suggest a possible role in tumour growth with supplemental nutrition and, conversely, starvation, energy reduction and protein-free diets have produced a reduction in tumour growth in certain experimental models⁷⁹.

There is a paucity of evidence for *in vivo* stimulation of tumour growth in humans by nutrition, although a reliably accurate assessment of tumour growth *in vivo* is difficult using the techniques currently available. Growth may also be assessed in terms of protein metabolism because it requires an increase in protein content, which in turn is dependent on the balance between protein synthesis and degradation. Theoretically, therefore, growth could be achieved by either an increase in protein synthesis or a decrease in protein breakdown, either of which would result in an increase in protein content. However, in malignant and transformed cells, growth is effected by an increase in protein synthesis rather than a decrease in breakdown⁸⁰⁻⁸². Protein synthesis is, therefore, a primary determinant of cellular growth and, in further studies in humans *in vivo*, correlated significantly with the expression of both the nuclear activation antigen⁸³ Ki67 and the proliferating cell nuclear antigen⁸⁴, which are recognized markers of cellular proliferation⁸⁵.

Mullen *et al.*⁸⁶ measured tumour protein synthesis rates and demonstrated that in patients with gastrointestinal cancer there was no difference in rates in groups receiving adequate parenteral ($n = 13$) or inadequate oral ($n = 12$) nutrition. Patients were not randomized but were allocated to either group depending on whether they could take food orally or required intravenous feeding. The technique used to measure protein synthesis (constant infusion of [¹⁵N]glycine) is open to criticism on methodological grounds⁸⁷. Nixon *et al.*⁸⁸ found neither clinical nor biochemical evidence of tumour growth in patients with metastatic colorectal carcinoma when patients were fed intravenously ($n = 55$) or orally ($n = 61$). Similarly, Shamberger *et al.*⁸⁹ found no difference in survival when patients with metastatic or locally advanced sarcomas were fed orally ($n = 18$) or intravenously ($n = 14$); the intravenous nutrition provided approximately 300 per cent more calories and 600 per cent more nitrogen than the oral diet. These studies suggest that nutritional support does not stimulate tumour growth, although the indices of growth assessed were relatively crude and reflect the limitations of current methodology.

The effect of nutrients on tumour protein synthesis in patients with localized colorectal cancers has been investigated⁹⁰. Patients were allocated to one of two groups, being either fasted for 24 h ($n = 9$) or given an intravenous feeding regimen for 20 h ($n = 9$) consisting of a standard amino acid source and glucose. A significant increase in protein synthesis was found in tumour biopsies from patients receiving intravenous nutrition, suggesting that tumour growth responded to the supply of exogenous nutrients, although evaluation of the effect of more prolonged periods of TPN would also be of interest. In a further *in vitro* study, in which the malignant cells themselves were isolated from the stromal cells of colorectal cancers, an 81 per cent increase in protein synthesis occurred when the cells were incubated in serum taken from the patients in the fed state compared with the fasted state⁹⁰.

Modulation of tumour growth by specific nutrients

Amino acids. A number of *in vivo* experiments in animals and *in vitro* studies using tumour cell lines have investigated the effect of specific amino acids on tumour growth. The incidence of spontaneously arising tumours is reduced in mice fed diets deficient in lysine⁹¹, but leucine restriction stimulated tumour growth⁹². Stimulation of growth has been reported in an AC33 rat tumour by the administration of leucine, isoleucine and valine⁹³, although leucine alone caused no stimulation of protein synthesis in other tumour cell lines⁹⁴. Glutamine

appears also to be of importance because it is utilized preferentially by many tumours⁹⁵ and the addition of this amino acid to tumour cells in culture in pharmacological doses has been shown to stimulate cell growth⁹⁶. In experimental tumour-bearing animals receiving TPN, the addition of Acivicin (Upjohn Pharmaceuticals, Kalamazoo, Michigan, USA), a general inhibitor of glutamine metabolism, resulted in a significant reduction in tumour growth⁹⁷. Some experimental tumour cells also demonstrate methionine dependency, being unable to proliferate and having a reduced metastatic potential when grown *in vitro* in the absence of this amino acid⁹⁸. The relevance of these experimental observations to humans is not clear and requires further investigation.

Branched chain amino acids. The role of branched chain amino acids (BCAAs) on protein synthesis in normal muscle has been studied by different groups. Although BCAAs or leucine alone can stimulate protein synthesis *in vitro*^{99,100}, there has been a failure to demonstrate this effect *in vivo*^{101,102}. Investigations on the administration of BCAAs to patients with cancer have compared BCAA-enriched solutions with standard amino acid solutions. Tayek *et al.*¹⁰³ found that in malnourished patients with cancer administration of a 50 per cent BCAA-enriched solution resulted in significant increases in the rate of whole-body protein synthesis and in the fractional rate of albumin synthesis.

The effect of BCAA-enriched solutions on human tumour protein synthesis has been studied *in vivo*, including the possibility that they may selectively modulate tumour growth. Patients with localized colorectal cancer were fed intravenously with either a BCAA-enriched solution or a standard isonitrogenous amino acid mixture; selective stimulation of tumour protein synthesis was observed¹⁰⁴. The BCAA-enriched solution caused a selective increase in tumour protein synthesis compared with the fasted state, but this was significantly lower than that induced by the standard nutritional regimen. This suggests that one of the non-BCAAs present in the standard amino acid mixture may have become rate limiting for protein synthesis; further studies are required to elucidate the mechanisms. Differential tumour stimulation *in vivo*, therefore, may be achieved by manipulating the composition of exogenous nutrients.

Arginine. Tumour cell lines need arginine for proliferation *in vitro*, and this amino acid is essential for the growth of certain tumours in rodents¹⁰⁵. The effect of increased arginine intake on tumour growth has been investigated in animals and in tumour cell lines, but conflicting results have been obtained with both a stimulatory¹⁰⁶ and an inhibitory^{107,108} effect having been reported. In a human breast cancer cell line, however, dibutylarginine has been shown to reduce tumour growth¹⁰⁹.

The metabolism of arginine (via the deiminase pathway) to nitric oxide has attracted research interest¹¹⁰. Nitric oxide influences the function of different cell types and although activation of the deiminase pathway results in an inhibition of experimental tumour growth, its effect on human tumours is unclear. Indeed, the resultant generated superoxides may actually enhance tumour growth¹¹¹. The effect of supplemental arginine on a human tumour cell line (A549) has been investigated¹¹². A significant increase in protein synthesis with arginine at defined concentrations was observed, but at high concentrations cellular toxicity and cell death occurred. Park *et al.*⁸³ investigated the role of supplemental arginine on human tumours in women with breast cancer. Patients were randomized to receive either a standard hospital diet or one supplemented with 30 g oral arginine per day for 3 days. Arginine supplementation resulted in a significant increase in tumour protein synthesis and increased expression of the activation antigen Ki67 by the breast carcinoma cells. This provides evidence, for the first time, for stimulation of human tumour metabolism *in vivo* by a large intake of a single dietary amino acid.

Different energy substrates. Over 50 years ago, Warburg demonstrated that tumours have raised rates of both aerobic and anaerobic respiration¹¹³. In addition, some tumours have increased glucose utilization and are susceptible to carbohydrate restriction¹¹⁴. Furthermore, some tumour cells are deficient in certain mitochondrial enzymes that utilize ketone bodies for energy production. Attempts have been made to modulate tumour growth by altering the energy substrates available to tumour cells. Studies *in vitro* have shown that the glucose antimetabolite, 2-deoxyglucose, has antitumour activity. Administration of this substance to rats reduced the growth of Walker 256 tumours cells¹¹⁵ and (also in rats) a ketogenic diet resulted in a reduction in tumour size and weight¹¹⁶. In humans, however, a ketogenic diet did not alter nitrogen balance or protein turnover compared with an isocaloric, isonitrogenous, non-ketogenic diet¹¹⁷. These measurements, however, were made on the whole patient and represent the sum of metabolic events in all tissues. The effect of this diet on the tumour itself remains uncertain and further studies are needed to investigate the effects of manipulation of the energy source on modulation of tumour growth in humans.

Essential fatty acids. The EFAs can be oxidized by normal cells into lipid peroxides, which are thought to play an important role in the control of cell division¹¹⁸. PUFAs are susceptible to lipid peroxidation, producing a range of oxygenated lipids and metabolites, e.g. malondialdehyde which is rigidly controlled in living tissues and closely linked to the rate of cell multiplication¹¹⁸. The reactive compounds produced are known to damage DNA and may play an important role in controlling cell division¹¹⁹. Studies of human tumour cell lines and experimental animal tumours have shown them to be resistant to lipid peroxidation^{118,119}. Biochemical analysis of these tumours has documented low levels of the 6-desaturated EFAs (*n*-6: GLA, arachidonic acid; and *n*-3: eicosapentanoic acid), and a compensatorily enhanced concentration of the monounsaturated oleic acid. A recent investigation of EFAs in human breast cancer revealed that the 6-desaturated PUFA content was lower in tumours giving rise to systemic metastases than in localized growths¹²⁰.

The addition of GLA and arachidonic acid to a variety of tumour cells in culture results in stasis and cell death; eicosapentanoic acid is particularly cytopathic to colonic cancer cell lines^{119,121} and GLA enhances the cytotoxicity of chemotherapeutic agents¹²². Cell damage and death appear to be mediated by enhanced lipid peroxidation, with increased production of malondialdehyde and related products^{119,121}. In some animals bearing mammary tumours addition of GLA to the diet inhibited tumour growth^{119,123}, although there is a paucity of data regarding human tumours. Sakaguchi *et al.*¹²⁴ recently documented reduced growth of human colonic cancer cell lines in nude mice fed a diet rich in *n*-3 PUFAs. Pilot studies carried out in patients with different types of advanced cancers (hepatoma, bronchial carcinoma) have recorded some tumour regression^{125,126}. Recent data have also suggested that GLA and eicosapentanoic acid can modulate growth of human tumours (breast, melanoma) transplanted into nude mice¹¹⁹.

Therapeutic implications

Provision of nutritional support (complete or selective) to a tumour-bearing host may induce or enhance tumour growth. However, nutritional stimulation of metabolic activity in tumour cells may increase their susceptibility to chemotherapy. Reynolds *et al.*¹²⁷ investigated the effect of the cell cycle-specific chemotherapeutic agent methotrexate on tumour growth in nutritionally supported rats. The animals were fed a protein-free diet for 10 days and then given methotrexate. The better response to therapy was in the group given oral nutritional repletion compared with the group maintained on a protein-free diet. A similarly enhanced response to chemotherapy was found in rats fed on continuous parenteral or intrajejunal feeding for 10 days before chemotherapy¹²⁸.

A study combining supplemental nutrition with doxorubicin (cell cycle-specific agent) and cyclophosphamide (cell cycle-non-specific agent) in a rat model with subcutaneously implanted AC33 mammary tumour found that in animals receiving pulsed TPN the antitumour effect of doxorubicin, but not cyclophosphamide, was enhanced¹²⁹. The same group demonstrated that the antitumour effect of methotrexate was also enhanced by pulsed TPN¹³⁰. The effect of TPN on AC33 mammary tumour cell kinetics has revealed that 2 h of TPN was sufficient to increase the number of cells in S phase with a corresponding decrease in the ratios of G0/G1 and G2/M tumour cell populations¹³¹. These changes occurred before any effect on tumour volume could be detected. However, the alteration of tumour cell kinetics was short lived, the cells returning to their original state after 24 h of nutrition. These results must be interpreted with caution before extrapolating to the possible effects of TPN on human cancer chemotherapy. The tumours in these animal models were rapidly growing with doubling times of 2–3 days, and resulted in death of the animals⁷³ within 6 weeks; this may not be representative of the situation in human cancers.

The sensitivity of human breast cancers to chemotherapy (e.g. doxorubicin, cyclophosphamide) is also dependent on the number of cells in the S phase of the cell cycle. Remvikos *et al.*¹³² demonstrated that patients with tumours with >10 per cent of the cells in S phase had an increased response to chemotherapy. Attempts have been made with human breast cancers to synchronize the tumour cell cycle (e.g. using hormones) before chemotherapy. These sequential combinations have resulted in apparent improvement in anticancer responses¹³³.

This approach of priming the cancer cell to the effect of chemotherapy, by provision of nutrients, has now been applied to the treatment of cancer in humans for the first time. It has been demonstrated that a 3-day pulse of oral arginine supplementation could stimulate human breast cancer protein synthesis and expression of activation antigens *in vivo*⁸³. As a result of these findings, patients with locally advanced breast cancer have been treated with neoadjuvant chemotherapy and arginine, with the amino acid being given orally for 3 days before initiation of chemotherapy. The preliminary results of this study look promising¹³⁴, with an increased response rate over historical controls¹³⁵, although further careful evaluation of this therapeutic approach is required.

Conclusion

Despite the numerous investigations performed over the past 20 years, the place of nutritional support in the management of malignant disease remains ill defined, although some generalizations can be made. The conventional indication for providing supplemental nutrition has been to increase body-weight and muscle mass, and to reduce mortality and morbidity in the patient with cancer undergoing surgery. The evidence suggests that perioperative nutritional support, if given for at least 10 days, may reduce morbidity and mortality in some patients. Although this subgroup has not been fully characterized, it probably represents those patients with biochemical evidence of severe malnutrition, manifest as a low serum albumin concentration and excessive weight loss. In contrast, there is no evidence that parenteral nutritional support benefits patients undergoing chemotherapy or radiotherapy in terms of an increased tumour response rate or prolongation of survival. It may even have a deleterious effect in patients receiving chemotherapy as it has been demonstrated to be associated with a reduced survival.

Current interest in metabolic support in patients with non-malignant disease who have lost weight is being directed towards alteration of the stress response (cytokines, prostaglandins, hormones), provision of specific fuels, and administration of certain growth factors¹³⁶. Similarly, in malignant disease current research is highlighting these three areas of

crucial importance. In the metabolite of leucine regulate protein as key regulators of both anti-skeletal and cardiac muscle. *J Biol* and control of nitrogen currently generating major interest. Certain amino acids, ribonucleotides and ribonucleotides have all been demonstrated to stimulate antitumour host defence mechanisms and some also modulate tumour cell metabolism. The use of a nutritional regimen that will not support tumour growth because it is depleted in certain key nutrients in combination with the administration of certain growth factors necessary for non-pathological tissue growth offers exciting possibilities for the innovative management of malignant disease.

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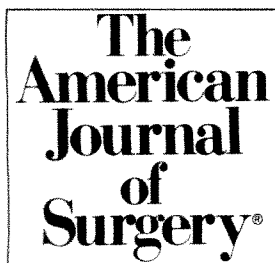
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The March issue of the Journal carried the first digest, of articles published in late 1991 and January 1992 in The American Journal of Surgery and identified by that journal's Editor, Dr Hiram Polk, as of particular interest. This month we highlight papers from February and March. A digest from the same issues of The British Journal of Surgery written by our Editor, Professor John Farndon, is to be published in the July issue of our American sister journal. Correspondence on the content of papers should be addressed primarily to the source journal, although we would be interested to receive a copy.

Biliary surgery

The February 1992 issue of the Journal examined an informative series of patients from the Queen Mary Hospital in Hong Kong with special reference to the palliation of malignant hilar biliary obstruction. There are few common problems in surgery that have been so resistant to clinical resolution¹. Edward Lai, John Wong and associates compared the results of operative ($n = 34$) and non-operative ($n = 16$) decompression. Patients undergoing drainage without operation had more medical problems and a lower serum albumin level initially (both $P < 0.03$). Whether the non-operative drainage treatment represented state-of-the-art endoscopic and radiological interventions is not clear, but these patients fared worse than those treated by choledochoenteric bypass with respect to in-hospital mortality ($P < 0.05$) and more frequent hospital readmission ($P < 0.02$). Individualization is obviously the answer, especially when one considers an honest assessment of the judgmental and technical skills of the interventional endoscopists and biliary surgeons in a given unit. No doubt more will be written on this subject and the preferred approach.

Sepsis

For more than a decade, numerous laboratories have reported work suggesting that 'non-specific' host defence enhancement would be helpful in the fight against infection. February's lead article assessed the efficacy of such a putative agent in a randomized prospective trial in 213 consecutive adults from three major trauma centres in the USA². The patients had an injury severity score > 20 and overt bacterial contamination but had presented for treatment promptly. Interferon gamma (IFN- γ) or a placebo was given daily to each patient for 10 days, following concepts previously reported³. Patients randomized to receive IFN- γ were slightly older and more severely injured ($P = 0.02$). By the third day those treated with IFN- γ manifested improved monocyte human leucocyte antigen (HLA)-DR antigen expression ($P = 0.0001$) which was maintained until after drug administration ended. Outcome was better in the treated patients than in those receiving placebo but not significantly so: there were nine deaths *versus* 12 and 17 major infections requiring drainage *versus* 22. Termination of IFN- γ treatment after 10 days was an apparent design error in this trial. Whether combination therapy will be a better answer or whether the drug should be given for longer and in a larger trial remains to be seen.

Endoscopy

The battle over control of the endoscope is waged quietly, or not so, all over North America. Reed *et al.* reported the experience of surgeons performing more than 1000 colonoscopies who had not been formally trained in this procedure⁴. A single perforation in 1025 diagnostic and therapeutic colonoscopies was described. This is clearly a good record but does not address important issues of the indications, accuracy

and costs. All of medicine in the USA is now being laid on the altar of cost containment. There is evidence that surgeons without formal training in colonoscopy perform it as well as (or better than) other medical specialists. While true, this observation may no longer be a case in point: the American Board of Surgery now requires significant endoscopic experience for its candidates for examination and the Society of American Gastrointestinal Endoscopic Surgeons has become our most rapidly growing national surgical organization.

Peptic ulcer disease

It is uncommon that a review article be highlighted in such a perforce, truncated summary of a journal's contents. Katz and Hollander, however, addressed the cost and efficacy issues germane to the industry of pharmacological treatment for peptic ulcer disease⁵. While there is a so-called 'bottom line', the essence of this paper is an elegant physiological review of decreasing gastric acidity, neutralization or suppression of acid production and the improvement of the protective and restorative properties of the gastric mucosa.

Hernia surgery

The modern management of groin hernia has been front and centre in the Journal for the past few years, especially among letters to the Editor. Gilbert describes a sutureless 'plug' approach with polypropylene mesh placed in the internal ring, but then proceeds to reinforce the posterior wall of the inguinal canal with a conventional swatch of the same material⁶. Both pieces are said to remain in place by internal forces and avoid the occasional damage to vital structures by sutures themselves. The author is a leader among the growing cache of hernia specialists in the USA whose methods are often adopted by many practitioners.

Wound healing

Surgical practice still evolves in direct, but often temporarily remote, relationships to advances in basic science. Growth factors have, indeed, proliferated not only in wounds but also in the surgical literature, and one will soon need a race-card to recognize the horses and their α , β , and γ variants. Notwithstanding the current confusion, the report by Hayward, Robson and associates is of more than passing interest⁷. One must first concede that bacterial contamination retards closure of most wounds, a fact that most experienced surgeons recognize. The authors found that recombinant human fibroblast growth factor provided healing of bacterially contaminated experimental burn wounds without any change in the density of bacteria on the burns. The potential for clinical use, if its value can be confirmed in a clinical trial, is enormous.

Trauma

Open pelvic fractures are ugly and unpleasant injuries regularly associated with severe contamination, devascularization of

tissue, avulsions, haemorrhage and shock. Sinnott, Rhodes and Brader described a good result in 20 such patients by emphasizing fundamental principles of care⁸. Although seen over 10 years, the basics of haemorrhage control, infection prevention or treatment, and radical debridement (including hemipelvectomy in two cases) resulted in the survival of 17 patients. On average these patients required 26 units of blood, nine operations each, and a hospital stay of 43 days, convincing the authors and the Editor that such patients should be cared for in proper trauma centres. Few will argue with that conclusion.

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Der Chirurg

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Following our exchange of digests with *Der Chirurg* in April, Professor Christian Herfarth and Dr Thomas Lehnert have this month prepared an overview of key papers appearing in that journal in the first quarter of this year. The July issue of *Der Chirurg* carries a reciprocal digest. Specific comments should be addressed primarily to Professor Herfarth, although a copy to *The British Journal of Surgery* would also be welcome.

Vascular surgery

Vascular reconstruction with a distal below-knee anastomosis is associated with a high rate of early graft occlusion; the literature reports rates exceeding 20 per cent. The reasons for this include high outflow resistance and technical errors. Vascular surgeons in Augsburg¹ studied prospectively the value of intraoperative techniques such as angiography, angioscopy, electromagnetic flowmetry and peripheral vascular resistance measurement in improving early graft patency rates in 50 patients undergoing below-knee reconstruction during a 14-month period. Forty-five of 50 distal anastomoses were crural; 18 reconstructions used non-reversed saphenous grafts or saphenous *in situ* procedures. All four stenoses distal to the bypass were detected by angiography and none by angioscopy because the small-calibre vessels did not permit insertion of the angioscope (outer diameter 2.2 mm). Bypass stenosis and incomplete valvulotomy were detected exclusively by angioscopy ($n=3$) whereas stenoses at the distal anastomosis ($n=3$) were visualized equally by angioscopy and angiography.

Intraoperative flow and outflow resistance measurements increased operating time by 5-10 min. Cut-off values derived from relative operating characteristic curves were 1600 peripheral resistance units and 140 ml/min. Outflow resistance measurements of crural bypasses had a specificity of 88 per cent, a sensitivity of 83 per cent and a positive predictive value of 96 per cent for 30-day bypass patency. Peripheral resistance measurement was a significantly better predictor of early graft occlusion than flow measurement. Additional tests using papaverine did not increase the discriminatory power of the test. The authors concluded that angioscopy is superior to intraoperative angiography for the detection of stenosis of the bypass segment and specifically for the detection of incomplete venous valvulotomy, but angiography is superior for the

detection of stenosis distal to the distal anastomosis. Outflow resistance measurement merits further evaluation, while bypass flow measurement had reduced predictive value for early graft patency.

Long-term results of aortoiliac reconstruction have been studied by the Mainz Vascular Surgery Group². In a retrospective study of 181 patients operated on with an aortodistal bifurcation graft for aortoiliac occlusive disease during an 11-year period (1976-1986), 130 patients were followed up (71.8 per cent). The 30-day mortality rate was 5.4 per cent. The mean follow-up was 65 (range 18-149) months. No further vascular reconstructions were required in 65 patients (78 per cent of the 83 still alive). Only five of 52 patients who had stage IIb disease before operation progressed to stage III whereas 25 of 52 patients improved to stage I or IIa. In contrast, only eight of 31 patients with stage III or IV disease improved to stages I or IIa. Duplex scanning revealed a proximal anastomotic aneurysm in 4 per cent of cases and a distal anastomotic aneurysm in 11 per cent. The 1-, 5- and 10-year survival rates were calculated as 87, 73 and 59 per cent, respectively. More than half of the patients died from myocardial infarction. Five of 47 patients who died succumbed to malignant disease and this group of patients may warrant close observation aimed at early detection of malignancy.

The acute abdomen

Acute-onset abdominal pain requiring an immediate decision of operative treatment remains one of the most severe diagnostic problems facing the general surgeon. Early studies evaluating a standardized diagnostic approach to these patients have been conducted in the UK, but not yet in Germany. Ohmann and associates³ reported experience acquired within the framework

of a European Community-supported prospective multicentre international study (The European Community Concerted Action on Objective Medical Decision Making in Patients with Acute Abdominal Pain). The two-phase study included a period in which the initial diagnosis (based on history and physical examination) supplemented diagnosis after additional procedures (ultrasonography, radiography, blood biochemistry) and post-treatment diagnoses were compared using standardized questionnaires.

In a test phase of the study the diagnostic procedure was amended by a standardized questionnaire and computer-assisted diagnosis using a program developed and tested by Adams and colleagues. Endpoints of the study were the accuracy of the initial and supplemented diagnosis, rate of perforated appendicitis, negative appendectomy rate, negative laparotomy rate, rate of missed indications for urgent operation and rate of delayed operation.

The study was conducted over a 15-month period at six hospitals. In all, 527 patients entered the basic study and 1254 the test phase. In the basic study, the diagnostic accuracy of the initial investigator was 59 per cent and that of the informed investigator 77 per cent. The negative appendectomy rate and the negative laparotomy rate were 13 and 7 per cent, respectively. Indications for urgent operation were missed in 1.1 per cent of patients and delayed in 3.4 per cent.

In the test phase, the diagnostic accuracy of the initial investigator was 59 per cent and of the informed investigator 78 per cent. The negative appendectomy rate and the negative laparotomy rate were 15 and 8 per cent, respectively. Indications for urgent operation were missed in 1.9 per cent of patients and delayed in 2.4 per cent.

The accuracy of computer-assisted diagnosis was 51 per cent; this was best for ulcer perforation (75 per cent), non-specific abdominal pain (70 per cent), biliary disease (67 per cent) and diverticulitis (65 per cent). Positive predictive values did not exceed 60 per cent for any diagnosis. The authors concluded that introduction of structured and standardized history taking and physical examination did not improve diagnostic accuracy. Currently available computer-aided diagnosis had not improved results.

Intra-abdominal sepsis

Treatment of peritonitis remains one of the most challenging surgical problems. Bartels *et al.* prospectively studied the clinical course and outcome of patients with intra-abdominal sepsis during a 7-year period⁴. A total of 46 variables were recorded in 184 patients with diffuse peritonitis treated during this period. Evaluation of risk factors was by univariate and multivariate analysis. The overall mortality rate was 48 of 184 patients (26.1 per cent). Where the source of intra-abdominal infection could be controlled surgically, the mortality rate was 9 per cent in 150 patients. No patient in whom surgical measures failed to control the source of infection survived. If primary laparotomy succeeded in controlling the cause of infection, the mortality rate was 6 per cent in 104 patients. If two or more operations were required to achieve control, the mortality rate rose to 25 per cent in 46 patients. Statistical analysis using a stepwise logistic regression model revealed that control of the septic focus at primary operation was the most important factor. Other significant prognostic parameters were the preoperative serum creatinine level, age > 70 years, and the presence of concomitant liver disease. None of the other factors studied was statistically significant.

Treatment of intra-abdominal sepsis is particularly demanding in patients with acute pancreatitis. In a study of 15 consecutive patients with acute necrotizing pancreatitis treated surgically between 1986 and November 1990, Hanisch and colleagues⁵ described results from their technique for open packing of the abdomen. Treatment was based on the creation of three intra-abdominal 'compartments'. After transverse laparotomy a clean upper compartment was produced by lifting

the stomach cephalad and wrapping the stomach, liver and spleen with greater omentum. A middle compartment consisting mainly of the bursa and extending retroperitoneally was packed with a cellophane-covered abdominal pack and left open. A third clean lower compartment was created by mobilization of the left hemicolon caudad to cover the small bowel. To achieve this, the taenia of the colon was sutured to the abdominal wall. The procedure was completed by gastrostomy and faecal diversion by colostomy or ileostomy. Depending on whether cholecystectomy had been performed, cholecystostomy or T tube drainage of the common bile duct was added.

Postoperative management included daily change of the pack together with digital evacuation of debris from the middle compartment and rinsing of the bursa with at least 3 litres Ringer's solution. Bleeding during bursa debridement was observed in one patient and injury to the colon in another. One patient developed a pancreatic fistula. Other complications were stress ulcer ($n = 1$) and incisional hernia ($n = 3$). This technique was felt to be advantageous because it should reduce the incidence of undrained intra-abdominal abscess formation and avoid colonic necrosis, which can occur from the use of drains. Given a mean Ranson score of 7.9 in 15 patients an overall mortality rate of 13 per cent ($n = 2$) argues for further evaluation of this procedure.

Inflammatory bowel disease

In a retrospective study, Steegmüller and associates⁶ attempted to identify risk factors for the surgical treatment of patients with Crohn's disease. Between 1980 and 1989, 301 patients were treated surgically for Crohn's disease of the small or large bowel. Thirty-six of 338 operations were emergency procedures for peritonitis ($n = 32$), bleeding ($n = 2$) or ileus ($n = 2$). No patient died after elective surgery. The mortality rate for emergency procedures was 6 per cent (two of 36); the overall mortality rate was 0.6 per cent in 338 operations.

Most emergency procedures were performed for free or sealed perforation of the terminal ileum ($n = 20$) or caecum ($n = 3$). Two patients required surgical treatment for toxic megacolon. Almost half of the emergency operations were completed as discontinuity resections ($n = 15$). None of 16 patients with a primary anastomosis undergoing an emergency procedure developed anastomotic insufficiency. Continuity of the gastrointestinal tract was restored by primary anastomosis following resection in 250 patients, ten of whom (4 per cent) developed anastomotic insufficiency. Other frequent post-operative complications included infection of the laparotomy wound with abscess formation ($n = 13$). At the time of operation 116 patients were receiving steroids; the complication rate of these was 16.4 per cent compared with 3.7 per cent in patients without concurrent steroid medication. The most frequent complication in patients on steroid treatment was abscess formation of the abdominal incision ($n = 10$). The incidence of anastomotic insufficiency was reduced from 5.9 per cent in the first half of the study period to 1.4 per cent in the second half and the authors relate this to routine orthograde bowel cleansing and perioperative antibiotic prophylaxis.

In another paper on Crohn's disease the general principles of current surgical treatment concepts were reviewed by Betzler and colleagues⁷. It was recommended that surgical treatment should attempt to maximize the length of small bowel preserved. Resection should be limited to macroscopically involved bowel and there is no need to achieve histologically free margins. Insertion of intra-abdominal drains should be avoided whenever possible and the need for such drains can be reduced by liberal use of pedicled omentum.

The importance of adequate preoperative preparation of elective patients using hypercaloric nutrition and preoperative antibiotic treatment in patients with septic complications is emphasized. Orthograde bowel lavage is limited to patients without significant stenosis in whom a left hemicolectomy is

planned. If a diverting stoma is required a loop ileostomy is preferred to a colostomy.

Special reference is made to fistulous disease. Minimal bowel-sparing resection of the fistula-bearing segment together with the more distal stenotic bowel segment is recommended. In patients with interenteric fistulae the bowel segment where the fistula originates is resected, but in the recipient bowel (which is often free of Crohn's disease) the fistula is only excised and the defect oversewn. The same principles apply to treatment of vesicoenteric and genitoenteric fistulae. In the latter situation the procedure is frequently supplemented by omentoplasty. Retroperitoneal fistulation requires immediate attention and early operation is required. Preoperative conservative treatment is limited to preparing the patient for surgery. No conservative treatment of retroperitoneal blind fistulae is attempted since life-threatening complications may rapidly develop. After bowel resection and excision of the fistula the defect is covered with an omental patch. In patients with perianal fistulae an attempt is made at conservative treatment to preserve sphincter function. If this fails, a limited bowel resection of the fistula-bearing colonic segment is performed. A simple loop ileostomy as the sole procedure is indicated only if the fistula originates from the rectum and if its treatment would require proctectomy in a patient with preserved sphincter function. Primary excision of the rectum is performed only if recurrent disease has destroyed continence and left the patient with incapacitating diarrhoea.

In a complementary survey, Eigler and Vogt⁸ reviewed treatment strategies for ulcerative colitis. In the emergency situation early intervention within 2 days of onset is recommended in patients with toxic megacolon. If subtotal colectomy is performed in these patients, later reconstructive procedures should be envisaged and care should therefore be taken to preserve the ileocolic artery. The same is true if total colectomy with proctectomy is to be performed in a patient presenting with profuse rectal bleeding. An ileostomy may be constructed either as an end or loop ileostomy if later pouch reconstruction is planned. If a subtotal colectomy with preservation of the rectum has been carried out, the latter should be excised either when pouch reconstruction is performed or – if no reconstruction is planned – as a separate procedure, since the excluded rectum carries a considerable risk of malignant change.

In an elective situation precise preoperative manometric evaluation of sphincter function is mandatory. Given the

potentially good results of ileal pouch construction, ileorectal anastomosis should be avoided because of the risk of malignant change in the retained rectum. Since successful ileoanal pouch construction relies particularly on good sphincter function, this procedure should not be attempted if preoperative studies indicate compromised function or if sphincter function cannot be recovered by conservative measures such as anal sphincter training. Old age does not preclude pouch construction, the operative details of which the authors describe. They recommend the use of a J pouch, which they construct with a pouch length of approximately 15 cm and a capacity of 200 ml.

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Heteroconjugated antibodies enhance lymphocyte-mediated tumour cell lysis *in vitro* and *in vivo*

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Covalent linkage of an antitumour antibody specific for a tumour cell surface antigen to an antilymphocyte antibody specific for the T lymphocyte receptor complex produces a heteroconjugated antibody that can activate and redirect cytotoxic T lymphocytes to lyse tumour cells. The ability of an antilymphocyte-antitumour heteroconjugate (500A2 × 96.5) to direct the lysis of murine melanoma cells by cultured murine lymphocytes was tested in vitro using a 4-h chromium release assay and in vivo with a tumour neutralization assay. In vitro, the addition of heteroconjugated antibody significantly increased tumour lysis by murine C3H/HeN lymphocytes (median specific lysis 82.7 per cent with lymphocytes plus heteroconjugate versus 9.5 per cent for lymphocytes alone, $P < 0.001$). In vivo, treatment with heteroconjugated antibody plus lymphocytes significantly reduced the development of pulmonary metastases after intravenous tumour administration (median number of pulmonary metastases 28.5 for combined treatment versus 250 for heteroconjugate or lymphocytes alone, $P < 0.001$).

Until recently, immunotherapy for cancer has depended on non-specific stimulation of the immune system with agents such as interferons, interleukin 2 (IL-2) and lymphokine-activated killer (LAK) cells¹⁻⁴. These have met with varying degrees of success, but have been associated with considerable toxicity owing to the high doses required to produce a tumour response. Selective stimulation of specific antitumour immune mechanisms should result in improved response rates with considerably lower toxicity.

Cytotoxic T lymphocytes are a subgroup of T lymphocytes possessing powerful and highly specific cytolytic potential. Cytotoxic T lymphocyte activity is normally limited by major histocompatibility complex (MHC) restriction and by a unique cellular antigen, so that cytotoxic T lymphocytes are activated only when this specific cellular antigen is presented in association with a self-MHC complex (Figure 1a). Under normal circumstances, very few cytotoxic T lymphocytes recognize any particular tumour antigen, and therefore the intrinsic immunity to tumour cells is very limited⁵. If this restriction could be bypassed and cytotoxic T lymphocytes targeted against specific tumour cells, many more cytotoxic T lymphocytes would be recruited into the immune response and antitumour immunity would be greatly enhanced⁶. It is possible to negate the MHC-antigen restriction by using certain anti-T lymphocyte antibodies. The T cell antigen receptor on the cell surface membrane is associated with a molecular complex of five proteins, called the CD3 complex. Antibody binding to the CD3 complex results in activation of the T cell without the need for MHC recognition^{5,7}. By covalently linking an anti-CD3 antibody to an antitumour antibody, a heteroconjugated antibody is produced. Using heteroconjugates consisting of anti-CD3 and antitumour components, activated cytotoxic T lymphocytes can be directed against any tumour cell bearing an antigen recognized by a specific antibody⁸ (Figure 1b). Using these heteroconjugated antibodies, cytotoxic T lymphocytes that would not normally lyse a particular tumour cell can be activated and recruited into the immune reaction to that tumour, greatly enhancing the natural immune response^{5,9-15}.

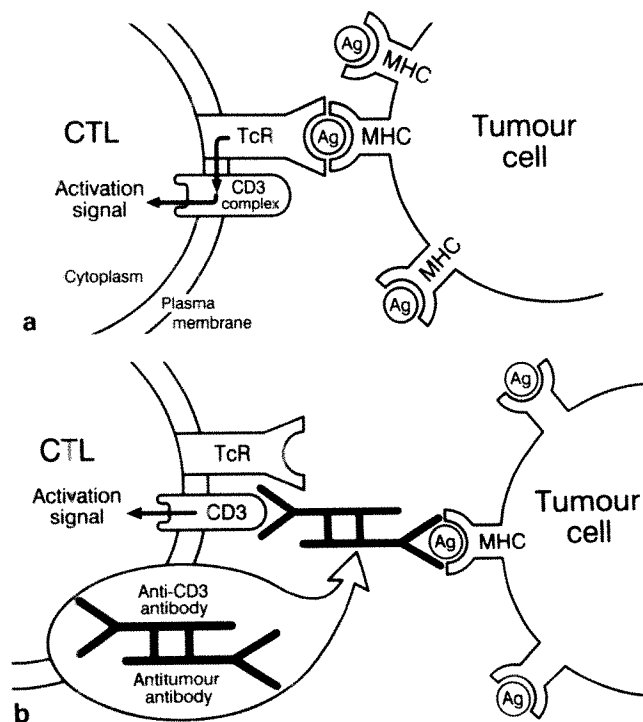


Figure 1 a Cytotoxic T lymphocyte (CTL) activation by tumour antigen. A tumour cell presents an MHC-antigen complex, which is recognized by the T cell receptor (TcR) on the CTL surface. An activation signal is generated and transduced into the cell cytoplasm via the CD3 complex, which is in close association with the TcR on the cell surface. Intracellular secretory granules then migrate to the site of contact with the target cell, fuse with the cell surface, and release a protein called perforin into the CTL-target cell junction. Perforin creates holes in the target cell membrane, resulting in a massive and lethal influx of Ca^{2+} ions into the target cell. b Heteroconjugated antibodies bypass MHC-antigen restriction of CTLs. A heteroconjugated antibody binding to the CD3 complex results in CTL activation without antigen binding to the TcR. The cytotoxicity of the activated CTL is then directed against the target cell specified by the antitumour part of the heteroconjugate. Any CTL to which the heteroconjugated antibody binds is thus activated against the tumour target, regardless of the specificity of the CTL encoded by its TcR. MHC, major histocompatibility complex; Ag, tumour antigen

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that recognize human tumour antigens are conjugated antibodies consisting of anti-CD3 antibodies linked to anti-CD3 antibodies have been used *in vivo* and *in vivo* using immunocompromised nude mice^{6,20}. Because few antibodies recognize animal tumour antigens, heteroconjugated antibodies have not been thoroughly evaluated in immunocompetent animals. Such investigation is critical in the development of this form of immunotherapy, as results from experiments using immunodeficient nude mice do not accurately predict the immune response in animals with a normal immune system.

This paper describes results using an anti-CD3-linked antitumour heteroconjugate (500A2 × 96.5) to target cultured cytotoxic T lymphocytes against tumour cells *in vitro* and in an *in vivo* tumour neutralization assay. These experiments used the K1735 mouse melanoma transfected with the human gene coding for the p97 antigen^{21,22}, a 97-kDa transferrin-like protein located on the outer surface of the plasma membrane of approximately 80 per cent of human melanoma cells²². The clone of tumour cells produced by this genetic manipulation (CL62) is a mouse melanoma that expresses a human surface antigen. This CL62 cell line is ideal for experimental use because it can be grown in immunocompetent mice and because several antibodies directed against the p97 antigen are available for heteroconjugated antibody production. The 96.5 antibody, which binds²¹⁻²³ to p97, was used in these experiments.

Materials and methods

Animals

Female C3H/HeN mice aged 8–12 weeks were purchased from Charles River Laboratories, Wilmington, Massachusetts, USA.

Antibody production

The 500A2 antibody used in these studies is a hamster antimouse antibody that binds to the CD3 receptor on murine T lymphocytes²⁴. 500A2 antibody was produced by intraperitoneal growth of the 500A2 hybridoma in nude mice. Mice were tapped daily once ascites had formed, and 500A2 was purified from pooled ascites, after centrifugation and sterile filtering, by passage over a protein-A column (Bio-Rad, Richmond, California, USA).

Purified 96.5 antibody, which recognizes the p97 antigen, was provided by the Oncogen Company (Seattle, Washington, USA).

Heteroconjugation

Heteroconjugate was prepared using a standard technique with *N*-succinimidyl-3-(2-pyridyldithio)-propionate forming covalent bonds between the 500A2 and 96.5 monoclonal antibodies as previously described^{18,25}. Dimers and polymers of the heteroconjugate were separated from monomers on two in-series Sephacryl HR300 gel filtration columns (Pharmacia, Uppsala, Sweden). The heteroconjugate was dialysed in phosphate-buffered saline and concentrated before use. The purity and molecular weight of heteroconjugates in the pooled fractions were assessed using sodium dodecyl sulphate polyacrylamide gel electrophoresis.

Effector cells

Fresh splenocytes were harvested under sterile conditions from C3H/HeN mice and plated in culture medium consisting of RPMI 1640 with 10 per cent heat-inactivated fetal calf serum, 2 mmol/l L-glutamine, 1 mmol/l sodium pyruvate, 0.1 mmol/l non-essential amino acids, 10 mmol/l *N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulphonic acid, 0.01 mmol/l 2-mercaptoethanol, 40 mg/l gentamicin, 100 units/ml penicillin and 100 µg/ml streptomycin. To select for the preferential growth and expansion of cytotoxic T lymphocytes, 100 units/ml human recombinant IL-2 (a gift from Hoffman-La Roche, Nutley, New Jersey, USA) and 0.5 µg/ml 500A2 were added to the culture medium. Cells were incubated for 5 days under these conditions at 37°C and 5 per cent carbon dioxide. To eliminate excess 500A2, cells were washed and replated in medium with IL-2 alone 48 h before use.

Tumour

The CL62 tumour line was kindly provided by Dr K. Hellstrom (Oncogen, Seattle) and maintained in culture in complete medium (RPMI 1640 with 10 per cent heat-inactivated fetal calf serum,

0.03 per cent L-glutamine, 100 units/ml penicillin and 100 µg/ml streptomycin).

Quantitative immunofluorescence

Effector cell populations were analysed after 7 days in culture on a FACS IV flow cytometer (Becton-Dickinson, Mountain View, California, USA). Cultured cells were evaluated for cell surface expression of Thy-1.2, a murine pan-T cell marker, using fluorescein isothiocyanate-labelled anti-Thy 1.2 antibody; Lyt-2, a marker of murine T suppressor/cytotoxic cells using fluorescein isothiocyanate-labelled anti-Lyt-2 antibody; and L3T4, a marker of murine T helper cells, using phycoerythrin-labelled anti-L3T4 antibody.

Cytotoxicity assay

Tumour target cells (2×10^6) were incubated at 37°C for 90 min with 150 µCi ⁵¹chromium (Amersham, Arlington Heights, Illinois, USA). Radiolabelled cells were washed, resuspended in medium and incubated for an additional 30 min at 37°C. After a final wash, ⁵¹Cr-labelled cells (4×10^3 cells in 0.1 ml per well) and antibody (0.08 µg per ml 500A2 or 96.5, or 0.16 µg per ml heteroconjugated antibody) were added to serially diluted effector cells in 96-well plates. Plates were centrifuged briefly and incubated at 37°C for 4 h. Supernatants were collected after further centrifugation and counted for ⁵¹Cr radioactivity. Cytotoxicity was calculated by the formula:

Percentage specific cytotoxicity

$$= \frac{(\text{experimental c.p.m.} - \text{spontaneous c.p.m.})}{(\text{maximal c.p.m.} - \text{spontaneous c.p.m.})} \times 100$$

Maximal lysis was determined by adding an equal volume of 5 per cent Triton X-100 (Sigma, St Louis, Missouri, USA) to target cells. Spontaneous chromium release values were determined by measuring the supernatant radioactivity after incubation of target cells in media alone. Triplicate samples for each data point were measured. Spontaneous release values were less than 30 per cent of the maximal c.p.m. for fresh tumour targets.

In vivo tumour neutralization

CL62 tumour cells were harvested from culture flasks with trypsin-ethylenediamine tetra-acetic acid, washed twice and resuspended at a concentration of 2×10^5 cells per ml in complete medium. Tumour cells were administered by tail vein injection in a volume of 0.5 ml per mouse. A dose of 10^5 tumour cells was reliably found to produce multiple pulmonary metastases.

During multiple tumour neutralization experiments, mice were divided into four treatment groups that received tumour plus 0.5 ml complete medium ($n = 34$), tumour plus 4×10^7 lymphocytes ($n = 23$), tumour plus 100 µg heteroconjugated antibody ($n = 25$), or tumour plus 100 µg heteroconjugated antibody and 4×10^7 lymphocytes ($n = 22$). Tumour cells were injected 5–10 min before the designated treatment. In all tumour neutralization experiments, mice received tumour plus treatment on day 1 and a second treatment on day 2. Mice were killed by ether inhalation 14 days after tumour injection and lungs were injected with India ink and destained with Fekete's solution to facilitate counting of lung metastases²⁶. The five lung lobes were separated and the number of pulmonary metastases per mouse counted under a dissecting microscope by an observer blind to the treatment group. Up to 250 metastases per mouse were counted: lungs with more than 250 metastases were simply designated as 'greater than 250'.

Statistical analysis

To analyse *in vitro* and *in vivo* data, treatment differences were assessed based on a Kruskal-Wallis test. As the data did not follow a Gaussian distribution, pairwise treatment comparisons were based on a Wilcoxon rank sum test. Multiple comparisons were made by applying the Bonferroni correction.

Results

Cell proliferation

This technique for culturing murine lymphocytes reliably produced a sixfold to tenfold expansion of cells over 7 days. Before culture, only 14 per cent of cells extracted from mouse spleens were Thy-1.2 positive (T cells). After 7 days in culture, flow cytometry showed 96 per cent of cells to be Thy-1.2 positive. Of these T cells, 5–10 per cent were L3T4 positive (T-helper cells) and 80–90 per cent were Lyt-2 positive (cytotoxic T lymphocytes).

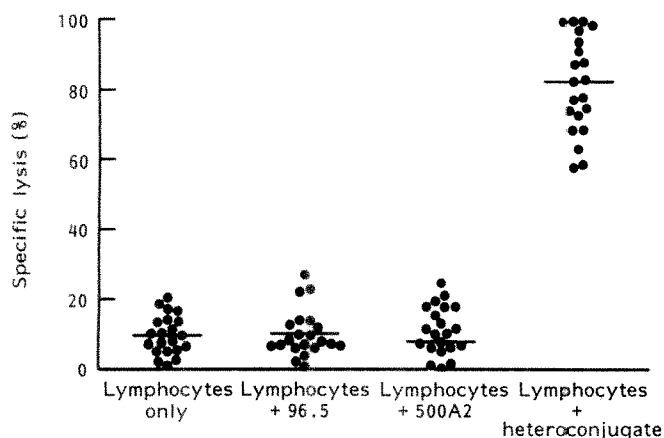


Figure 2 Enhanced lysis of CL62 tumour cells by cytotoxic T lymphocytes in the presence of the heteroconjugated antibody 500A2 $\times$ 96.5. CL62 cells were labelled with ^{51}Cr and incubated for 4 h with lymphocytes alone, lymphocytes plus the unconjugated antibodies 96.5 and 500A2, or lymphocytes plus the 500A2 $\times$ 96.5 heteroconjugate. Combined results from seven consecutive assays are shown. Bars are median values. $P < 0.001$ (lymphocytes plus heteroconjugate versus all other groups, Kruskal-Wallis test)

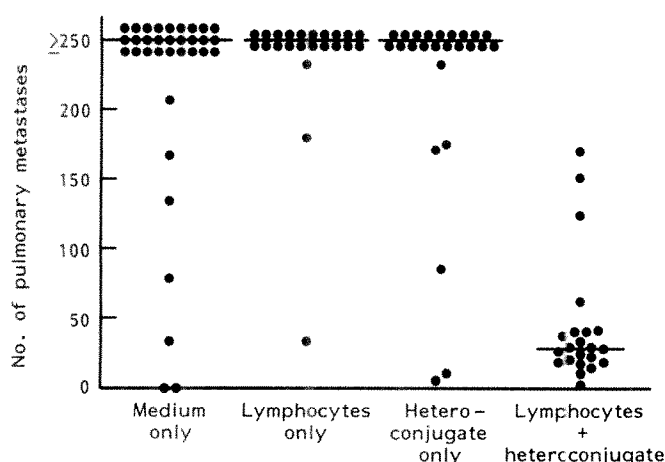


Figure 3 Pulmonary metastases at 14 days in mice treated with intravenous CL62 tumour. Mice treated with lymphocytes plus the heteroconjugated antibody 500A2 $\times$ 96.5 ($n = 22$) developed significantly fewer metastases than mice treated with medium only ($n = 34$), lymphocytes only ($n = 23$) or heteroconjugated antibody only ($n = 25$). Each point represents one mouse. Bars are median values. $P < 0.001$ (lymphocytes plus heteroconjugate versus all other groups, Kruskal-Wallis test)

In vitro cytotoxicity

Figure 2 shows the combined results of seven consecutive ^{51}Cr release assays. Non-specific lysis of ^{51}Cr -labelled CL62 by cultured murine lymphocytes alone was low (median 9.5 (range 0.8–20.3) per cent) at an effector:target ratio of 25:1. The addition of either 500A2 or 96.5 monoclonal antibody did not significantly increase tumour cell lysis (median (range) 7.8 (0–24.5) and 10 (0.5–26.9) per cent, respectively). The addition of heteroconjugated antibody with lymphocytes resulted in significant enhancement of tumour cell lysis (median 82.7 (range 57.8–100) per cent) at an effector:target ratio of 25:1 ($P < 0.001$).

In vivo tumour neutralization (Figures 3 and 4)

After the injection of 10^5 CL62 cells into the tail vein, multiple pulmonary metastases were present 14 days later in nearly all mice. In 34 mice treated with medium only, the median number of pulmonary metastases at 14 days was 250 (range 0–250). Similar results were demonstrated in 25 mice treated with heteroconjugated antibody alone (median 250 (range 5–250))

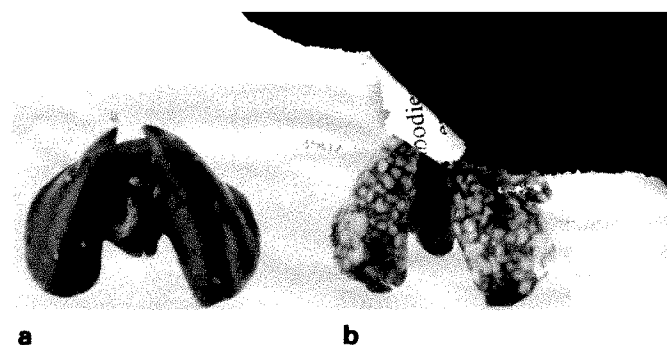


Figure 4 Treatment with lymphocytes plus heteroconjugated antibody significantly reduced the development of pulmonary metastases in mice after intravenous CL62 administration. Lungs were stained with India ink and then bleached with Fekete's solution, so that normal lung tissue appeared black and tumour deposits appeared white. **a** Isolated metastases in lungs from a mouse treated with lymphocytes and heteroconjugated antibody. **b** Multiple pulmonary metastases in lungs from a mouse treated with medium only

and in 23 mice treated with lymphocytes alone (median 250 (range 33–250)). For mice treated with lymphocytes plus heteroconjugated antibody ($n = 22$), the median number of metastases at 14 days was 28.5 (range 2–170). The difference in the number of pulmonary metastases between the group treated with lymphocytes plus heteroconjugated antibody and each of the other three groups was highly significant ($P < 0.001$).

Discussion

Immunotherapy represents a new and exciting treatment method, although until recently trials with immunotherapeutic agents have focused on non-specific stimulation of the immune system, most notably with IL-2 and LAK cells^{2,4}. Attempts to direct the immune response against specific tumour targets began with the use of monoclonal antibodies to tumour antigens. Monoclonal antibodies have recently been used in clinical trials for the treatment of solid tumours, but to date they have been ineffective against established tumours^{27,28}. Tumour-infiltrating lymphocytes represent another form of tumour-specific therapy. In theory, lymphocytes isolated from within tumour tissue will possess a high proportion of T lymphocytes with specific cytotoxicity against that particular tumour. Tumour-infiltrating lymphocyte therapy involves the isolation and expansion of such tumour-specific T lymphocytes from excised tumour tissue by *in vitro* culture with IL-2, and the subsequent reinfusion of cultured tumour-infiltrating lymphocytes into the patient. Initial clinical studies with tumour-infiltrating lymphocytes have reported promising results^{29–32}. Tumour-infiltrating lymphocytes require several weeks of *in vitro* expansion before sufficient cell numbers for patient therapy can be generated^{33–35}. They cannot be generated from all tumours and not all tumour-infiltrating lymphocyte cultures possess specific cytotoxicity against their tumour of origin^{33,36–38}.

A new approach to cancer immunotherapy involves specific stimulation of the subset of T lymphocytes possessing antitumour activity, the cytotoxic T lymphocytes. The use of heteroconjugated antibodies consisting of an anti-T cell antibody covalently linked to an antitumour antibody has allowed the direction of cytotoxic T lymphocytes against specific tumour cells. The 500A2 $\times$ 96.5 heteroconjugate significantly enhanced *in vitro* lysis of the CL62 melanoma line by murine cytotoxic T lymphocytes, but *in vitro* cytotoxicity does not correlate well with *in vivo* antitumour efficacy. It was decided, therefore, to assess these heteroconjugated antibodies *in vivo*. As an initial step towards this goal, a tumour neutralization model was used in which tumour cells and treatment are administered consecutively by tail vein injection into laboratory mice. The clinical relevance of such tumour neutralization studies is limited. It was found that heteroconjugated antibodies were effective in preventing tumour

growth under these optimal conditions, but current work is directed at the treatment of established tumours.

Previous *in vivo* experiments with heteroconjugated antibodies have used cultured human lymphocytes and nude (*nu/nu*) mice^{6,20}. The nude mouse lacks T lymphocytes, however, and is unable to mount a T cell immune response. An immunocompetent mouse strain, such as the C3H/HeN mouse used in this study, provides a much more realistic assessment of the *in vivo* effects of heteroconjugated antibodies. Syngeneic C3H/HeN lymphocytes, rather than human lymphocytes, can be used as effector cells, after *in vitro* culture under conditions that result in the selective proliferation of cytotoxic T lymphocytes. These conditions include the addition of human recombinant IL-2 and 500A2, an anti-CD3 immunoglobulin G antibody, which is also responsible for directing cellular lysis when incorporated into heteroconjugated antibodies²⁴.

Mice treated with a combination of cultured lymphocytes and heteroconjugated antibody had a significant reduction in pulmonary metastases compared with the other three experimental groups. Although the majority of animals in this study developed large numbers of pulmonary metastases after intravenous tumour injection, a small number of mice developed only a few metastases and two of 82 control mice (2 per cent) had no detectable tumour growth. The K1735 tumour originated in C3H/HeN mice, and is therefore identical with respect to MHC genes. Because this is a syngeneic tumour, it will grow in C3H/HeN mice without eliciting an immune response, in contrast to xenogeneic or allogeneic tumours, which would be rejected. However, the transfection of the human p97 antigen into the K1735 tumour results in an incidence of tumour rejection that is directly related to the level of p97 expression on the cell surface²¹, and transfected clones with very high levels of p97 expression fail to grow at all in immunocompetent C3H mice. The particular clone of transfected cells used in these experiments (CL62) reliably produces multiple pulmonary metastases in C3H mice, but is associated with up to 10 per cent spontaneous tumour rejection caused by an immune response to the p97 antigen (K. E. Hellstrom, personal communication). In keeping with this finding, the results show that eight of 82 control animals (10 per cent) developed fewer than 100 pulmonary metastases after intravenous injection of CL62. Despite this spontaneous rejection rate, combination immunotherapy with heteroconjugated antibodies and activated cytotoxic T lymphocytes had a significant inhibitory effect on the development of metastases.

This paper describes initial results in extending *in vitro* work to an *in vivo* animal model. In designing this tumour neutralization model, a treatment regimen likely to provide the maximum antitumour effect was chosen. For this reason, mice were treated on two consecutive days with a large dose of heteroconjugated antibody (100 µg per mouse) and a dose of lymphocytes (4×10^7 per mouse) that approximates to the maximum number of lymphocytes that can be administered in 0.5 ml. The lymphocyte:tumour cell ratio of 400:1 present in the initial treatment is therefore far above the maximum effective *in vitro* ratio. In future studies, the *in vivo* efficacy of lower doses of heteroconjugated antibody and of effector cells will be assessed.

Although there was not complete neutralization of tumour growth in these experiments, a more prolonged treatment schedule might achieve total tumour ablation. Alternatively, metastases developing in mice treated with heteroconjugated antibodies and lymphocytes may represent selective growth of tumour cells that have reduced or absent expression of the p97 antigen. This possibility is being explored by the immunohistochemical staining of residual lung metastases for the p97 antigen. If heterogeneity of target antigen expression is responsible for tumour resistance to treatment with heteroconjugated antibodies, one option is to use a combination of heteroconjugates specific for two different tumour antigens, for

example the p97 and GD3 ganglioside antigens expressed on human melanoma cells^{22,39}.

Clinical studies with murine monoclonal antibodies (including 96.5) in patients with metastatic melanoma have demonstrated that such antibodies can safely be administered by intravenous infusion, and localize well to tumour sites³⁹⁻⁴¹. Because treatment with heteroconjugated antibodies will almost certainly require multiple infusions, and as most monoclonal antibodies to tumour antigens are derived from murine hybridomas, the development of an antimouse immune response is a potential problem. Human antimouse antibody may form high molecular weight complexes with injected murine antibodies, resulting in rapid blood clearance, high hepatic and splenic uptake and reduced tumour targeting. The use of human rather than murine monoclonal antibodies will probably provide the ideal solution for human therapy⁴². The most immunogenic part of the immunoglobulin molecule is the Fc region, and it is possible to construct antibodies consisting of a murine antigen-binding ($F(ab')_2$) segment but with a human Fc region. These chimeric antibodies are less likely to provoke an antimouse response than are intact murine immunoglobulins⁴³. Bispecific antibodies can be produced by linking two murine $F(ab')$ fragments with specificities for different target antigens, without an Fc region⁴⁴.

Heteroconjugated antibodies have immense potential for use as immunotherapy for human tumours. This study demonstrated that tumour cell lysis is enhanced by heteroconjugated antibodies *in vitro* and in an *in vivo* tumour neutralization model in a syngeneic murine tumour model.

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Use of Teflon stents for lymphovenous anastomosis

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The treatment of lymphoedema is difficult; conservative and surgical management show variable results. Lymphovenous anastomoses (LVAs) in experimental animals and patients give poor results in the treatment of primary lymphoedema and variable results in that of secondary lymphoedema. Conventional sutured LVAs were compared with anastomoses using polytetrafluoroethylene (Teflon) stents; 32 sutured and 21 stented LVAs were constructed in 16 rabbits with normal lymphatics. Anastomoses were assessed for quality and patency at 1–16 weeks by direct exposure; 27 cases were further assessed using lymphangiography. Patency in stented and sutured LVAs was 71 and 38 per cent at 1 week, and 38 and 8 per cent at 3 weeks, respectively. After 4 weeks all anastomoses were occluded. The quality of stented LVAs seemed to be higher than that of sutured LVAs. Stented LVAs are feasible and probably superior to conventional sutured LVAs. However, the patency of LVAs is of short duration because of the disadvantageous pressure gradient from lymphatics to veins, and this limits their clinical application.

The management of obstructive lymphoedema is a largely unsolved problem. Initial management is usually conservative, because the results of surgery are generally unsatisfactory. Conservative management consists of elevation, massage, and the use of high-pressure, graduated elastic stockings.

Surgical management can be broadly divided into palliative, excisional operations, such as the Charles^{1,2}, Thompson^{2,3} and Homans⁴ procedures, which are used when there are no functioning lymphatics, and operations designed to be curative, such as the enteromesenteric bridge operation⁵ which can sometimes be used when there is a localized obstruction. Most bypass operations involve the formation of either lympho-lymphatic or lymphovenous anastomoses (LVAs)⁶, using either lymphatics^{6–9}, lymph nodes¹⁰ or tissue pedicles¹¹.

The results of previous studies of LVAs in animals with or without experimentally induced lymphoedema and in patients with either primary or secondary lymphoedema have a number of common features. LVAs in the hind limbs of dogs with surgically induced lymphoedema have patency rates of 80–100 per cent up to 1 week^{12–15}, but decreasing rates thereafter, varying between 67 per cent at 6 months¹², 33 per cent at 8 months¹⁵ and in one study zero at only 3 weeks¹⁴. Lympholymphatic anastomoses in a similar animal model appear to give better results, from 100 per cent patency at 1 month¹⁶ to 50–75 per cent patency at 6 months¹⁷.

The reported results of sutured LVAs in patients with secondary lymphoedema are very variable^{18,19} and of doubtful significance; all can be criticized for their methodology and assessment criteria. The 'improvement' of lymphoedema cannot be attributed to patent anastomoses without objective evidence of patency^{19–21}. Nevertheless, a technique for LVA that gives good long-term patency might be of considerable clinical value and would certainly be worthy of clinical trial.

This paper describes the results of using a stent technique for LVA. Such a technique of vessel anastomosis using an external tubular stent dates back almost 100 years and a number of materials, from glass and ivory to modern plastics, have been tried; however, it has previously been used only for anastomoses during experimental surgery. In this study normal lymphatic vessels have been joined to normal veins. The reasons are twofold: first, because the production of lymphoedema in an experimental animal is difficult and time-consuming; and second, because the non-oedematous leg is a more rigorous

testbed for an experimental anastomosis as the pressure gradient between lymphatic and vein is lower.

Materials and methods

Sutured or stented LVAs were constructed between tributaries of the popliteal vein and an adjacent lymphatic in the hind limbs of 16 rabbits weighing between 2600 and 4242 (mean 3560) g anaesthetized with intramuscular Hypnorm (Janssen Pharmaceuticals, Oxford, UK) 0.5 ml kg⁻¹ (1 ml contains 0.315 mg fentanyl citrate and 10 mg fluanisone).

Initial preparation

A volume of 0.5 ml 5 per cent patent blue-violet dye was injected into the subcutaneous tissue of the hind paw and the paw massaged. A suitable tributary of the popliteal vein was exposed through a 2.5-cm longitudinal incision and a 1-cm segment dissected free from the surrounding tissues. The distal end of this segment was then ligated and divided. An adjacent lymphatic made visible by the dye was also mobilized for 1 cm, and divided proximally so that its free end lay adjacent to the upstream end of the divided vein (*Figure 1a*).

Sutured anastomoses

A short length of a 6/0 polypropylene suture was inserted into the lumens of both lymphatic and vein, to align and approximate the ends and act as a guide while suturing (*Figure 1b*). The vein was sutured to the lymphatic with simple interrupted 10/0 polypropylene sutures using $\times 20$ magnification; six to nine sutures were required. The intraluminal splint was removed before the last two sutures were tied (*Figures 1c and d*). Patency was confirmed by squeezing the paw to increase lymph flow and watching the blue-stained lymph flow through the anastomosis into the vein (*Figure 2*). Stainless steel marker clips were placed around the vein, 1 cm proximal to the anastomosis (*Figure 1e*).

Stented anastomoses

The stents were made from a 1.5-mm segment of a 21-Fr polytetrafluoroethylene intravenous cannula (outer diameter 0.8 mm, inner diameter 0.6 mm; Venflon 2, POC Health Care, Helsingborg, Sweden). Two small flanges were fashioned at one end (*Figures 3 and 4*). A 6/0 polypropylene suture was placed in the lumen of the lymphatic to act as a guide and to keep its walls apart. Two 10/0 sutures were inserted through opposite sides of the lymphatic (180° apart) and left untied (*Figure 3a*). These two sutures were then passed through the stent and used to pull the lymphatic through it (*Figure 3b*). The end of the lymphatic was turned back over the outside of the stent and the sutures tied around the flanges that had been cut at the other end of

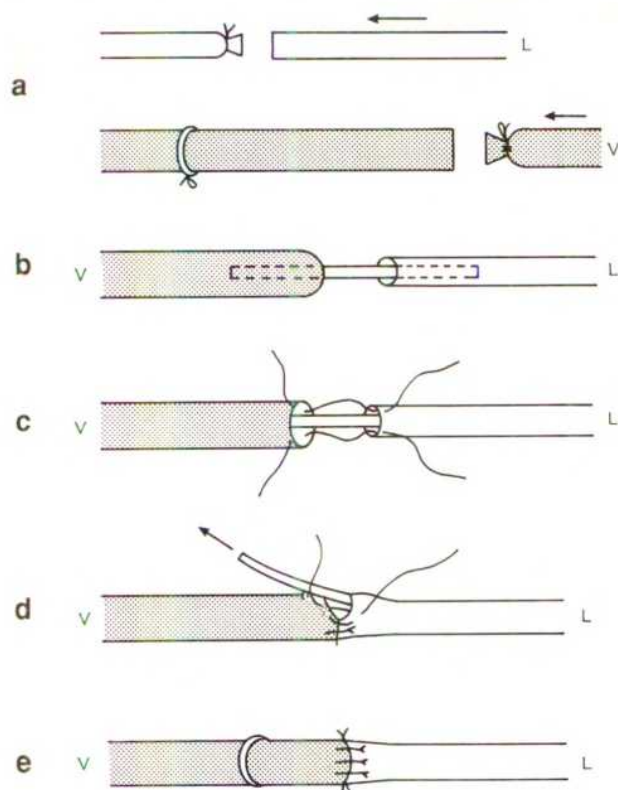


Figure 1 a Initial preparation for lymphovenous anastomosis, and b-e the procedure of sutured lymphovenous anastomosis. V, vein; L, lymphatic



Figure 2 Sutured lymphovenous anastomosis. Lymphatic (L) on the right and vein (V) on the left. Interrupted 10/0 sutures are visible; both vessels are filled with lymph. (Original magnification $\times 20$)

the stent to keep the everted cuff of lymphatic firmly in place (Figure 3c). Two more 10/0 sutures were then placed between the original two sutures and also tied around the flanges (Figure 3d). The 6/0 intraluminal splint was removed, and a 10/0 suture was placed through the back wall of the vein and the underlying fascia to fix the end of the vein to the adjacent tissues (Figure 3e). The stent was then pushed into the vein, well beyond the everted cuff of lymphatic and one or two 9/0 polypropylene circumferential sutures tied around the vein to hold it on to the stent. The suture at the back of the vein was then divided (Figures 3f and 5). After checking patency by squeezing the paw, a wire clip was placed 1 cm proximal to the anastomosis. All other visible adjacent lymphatics were ligated or coagulated and the wound closed in layers.

Assessment of the quality of the anastomosis

The quality of each anastomosis was assessed at the end of the operation according to the following criteria:

- Good – fully patent anastomosis without leakage; minimal vessel damage and good apposition of ends;
- Fair – fully patent anastomosis with minimal leakage; some vessel damage;

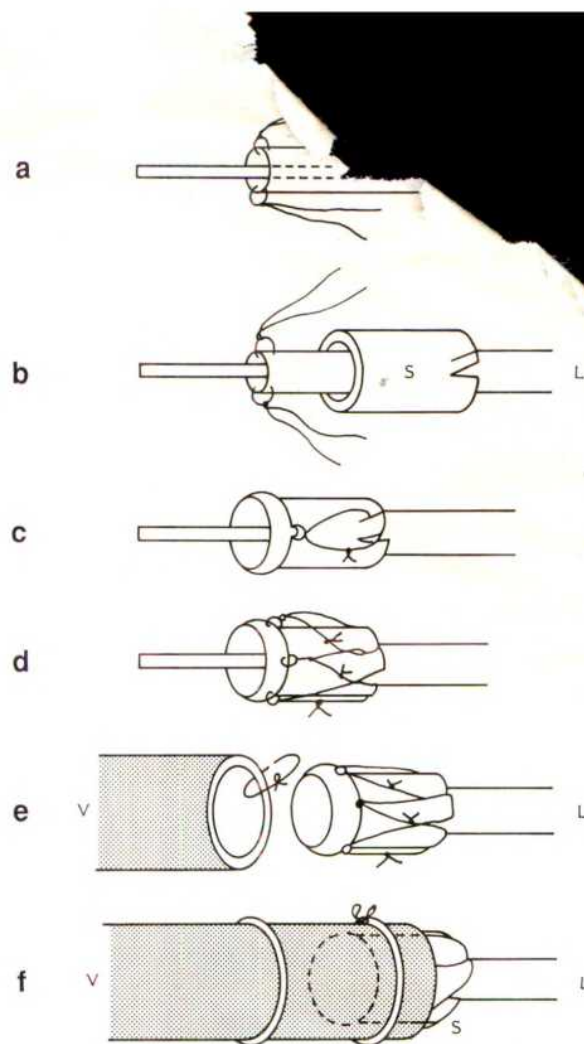


Figure 3 Procedure for stented lymphovenous anastomosis. V, vein; L, lymphatic; S, stent

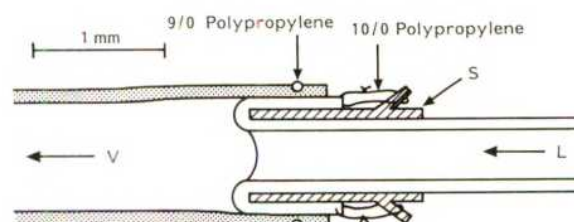


Figure 4 Longitudinal section of complete stented lymphovenous anastomosis. V, vein; L, lymphatic; S, stent

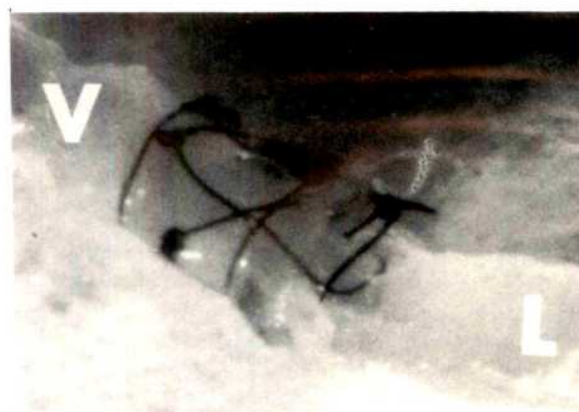


Figure 5 Stented lymphovenous anastomosis. Lymphatic (L) on the right and vein (V) on the left, showing cuffed back lymphatic with 10/0 ties. A flange on the stent is visible and two circumferential 9/0 ties; both vessels are filled with lymph. (Original magnification $\times 20$)

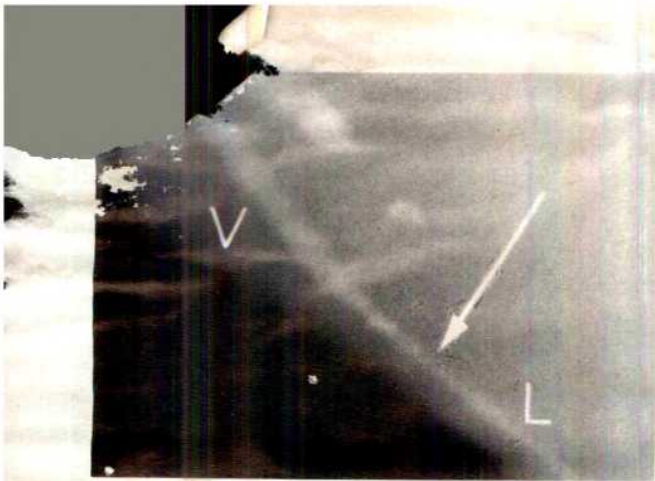


Figure 6 Lymphovenogram of stented lymphovenous anastomosis taken at 2 weeks. Lymphatic (L) in the lower leg, showing flow of contrast medium (Lipiodol) through the stent (arrowed) and into the vein (V). A wire clip (visible edge-on) placed around the vein, 0.5 cm proximal to the stent, can be seen, together with another clip more centrally, marking a second non-opacified anastomosis

Poor – patent but probably narrow anastomosis, or one with damaged and/or poor apposition of the vessel ends. Any anastomosis that was obviously occluded was refashioned or revised. Thus all anastomoses entered into the study were patent when the skin wound was closed.

Assessment of late patency

Three techniques for assessing late patency were used:

1. Injection of Lipiodol (May and Baker, Dagenham, UK) into a distal paw lymphatic, without exposing the site of the anastomosis, and taking radiographic lymphangiograms.
2. Injection of Lipiodol into the lymphatic used for the anastomosis, 2 cm distal to the anastomosis, after exposing the site of the anastomosis, and taking radiographic lymphangiograms (Figure 6).
3. Injection of patent blue-violet dye into the subcutaneous tissue of the paw after exposing the anastomosis, squeezing the paw and watching the passage of the blue-stained lymph through the anastomosis.

Results

Fifty-three LVAs were fashioned in 16 rabbits, 32 with the suture technique and 21 using the stent. In ten animals two anastomoses were performed in each hind limb; seven of these animals had two stented and two sutured anastomoses and three animals had one stented and three sutured anastomoses. One animal had one stented anastomosis in one limb and two sutured anastomoses in the other limb. In the remaining five animals only one anastomosis was performed in each leg; in three these were both sutured, in one both stented, and in one, one anastomosis was stented and one sutured. Lymphangiograms were performed between 7 days and 16 weeks on 27 anastomoses, 15 of which had been sutured and 12 stented. Some anastomoses were assessed on more than one occasion.

Technical assessment (Tables 1 and 2)

'Good' anastomoses were obtained in 17 (53 per cent) of the 32 sutured and 12 (57 per cent) of the 21 stented anastomoses. There were more 'poor' results in the stented group, probably as a result of a learning process. Although the numbers are small, the findings in Table 2 suggest that the site of the anastomosis affected the quality of the stented LVAs, the proportion of 'good' anastomoses being greater on the medial side of the leg where the lymphatics were larger and more closely matched the size of the stent.

Learning curve

There was no learning curve for the sutured anastomoses as the surgeon (N.J.S.) had practised this technique frequently before the study began, and so the quality of the sutured LVAs remained constant throughout the project, with eight of the

Table 1 Quality of lymphovenous anastomoses at end of operation

	Stented (n = 21)	Sutured (n = 32)
Good	12	17
Fair	4	14
Poor	5	1

Table 2 Quality of lymphovenous anastomoses at end of operation related to anastomotic site

	Stented (n = 21)		Sutured (n = 32)	
	Medial	Lateral	Medial	Lateral
Good	10	2	6	11
Fair or poor	3	6	5	10

Medial and lateral refer to the medial or lateral side of the leg

Table 3 Long-term patency of lymphovenous anastomoses

Time of assessment (weeks)	Stented (n = 21)				Sutured (n = 32)			
	No. assessed*	P	S	O	No. assessed*	P	S	O
1	7	5	2	0	8	3	3	2
2-3	13	1	4	8	13	0	1	12
4-16	8	0	0	8	14	0	0	14

*Some anastomoses were assessed on more than one occasion. P, Definitely patent; S, probably patent, but stenosed; O, occluded

first 16 and nine of the second 16 graded as 'good'. In contrast, only three (27 per cent) of the first 11 stented LVAs were 'good', compared with nine of the last ten. This improvement was due mainly to the gradual refining of the technique and the site chosen for the anastomosis. The sutured anastomoses usually took 50 min, the stented anastomoses 35 min.

Patency

Table 3 shows the long-term patency rates. At 1 week, five of seven (71 per cent) of the stented anastomoses that were assessed were definitely patent, compared with three (38 per cent) of the eight sutured anastomoses that were assessed. However, no stented anastomoses were definitely occluded, whereas two of the eight sutured anastomoses were. At 2-3 weeks, five of 13 (38 per cent) of the stented anastomoses, compared with one of 13 (8 per cent) of the sutured anastomoses, were patent or probably so. At or after 4 weeks, all anastomoses were occluded.

Discussion

The published studies of LVAs suggest that the critical factors determining patency are the nature of the surgical technique and the intralymphatic and intravenous pressures. Normally, lymphatic pressure is lower than venous pressure, although the lymphatic pressure in chronic lymphoedema may be higher²². After decompression by LVA, whatever the underlying abnormality, the pressure gradient is restored to normal, leading to reflux of blood into the lymphatic, thrombosis and eventual occlusion of the anastomosis^{10,13-15,20,21}.

This study shows that the use of a Teflon stent, even in a small animal such as the rabbit, is technically feasible and gives results probably superior to those from conventional suturing. It may have a better short-term patency rate, does not damage the luminal endothelium (any traumatized sections being exteriorized over the stent), provides a smooth and continuous endothelial surface between lymphatic and vein, holds the lymphatic lumen open, and places no foreign material within

the lumen. It is also technically less demanding and faster to perform. In humans, with larger lymphatic vessels, the procedure should be easier and quicker.

Nevertheless, all forms of anastomosis between lymphatics and veins are eventually confronted by two problems: the higher pressure in the veins and the subsequent occlusion of the anastomosis by thrombus and fibrosis. Initial histological studies, not reported here, suggest that collapse and fibrosis of the lymphatic, with regrowth of new lymphatics bypassing the anastomosis, is more common than the presence of thrombus. Whatever the mechanism of occlusion, the duration of patency after decompression of hypertensive lymphatics is short. Until this problem is solved or avoided, the clinical application of LVA will be limited.

Acknowledgements

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Abdominal aortic aneurysm, glaucoma and deafness: a new familial syndrome

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Several reports have suggested a genetic basis for the distribution of abdominal aortic aneurysm (AAA) in some families. The familial clustering of this disease is further demonstrated in this report of ten siblings, five of whom have confirmed AAA. This is the largest cluster so far reported. The majority of patients in this family group also have glaucoma and/or deafness.

There is increasing evidence for a familial distribution for abdominal aortic aneurysm (AAA). This paper reports the results of a study of AAA made on a group of siblings. The distribution of associated conditions is also discussed.

Patients

The family studied comprised ten siblings, one of whom, aged 69 years and suffering from deafness and glaucoma, underwent operation for AAA in this unit. He showed no sign of Marfan's syndrome. Other surviving siblings were contacted directly or via their general practitioner.

Results

Table 1 summarizes the findings of the survey. Sibling 1 was unable to travel to see us or his general practitioner. Sibling 2 had died 3 years earlier aged 79 years from an unknown cause. He had at one time undergone aortic aneurysm repair, was deaf, and had glaucoma. Sibling 3 had died 2 years earlier aged 79 years from a ruptured aortic aneurysm. Sibling 4 is 79 years old, has glaucoma and is deaf; she does not have AAA. Sibling 5 is 77 years old but could not be contacted (address unknown). Other siblings reported that he is partially deaf and has glaucoma; they did not know whether or not he has AAA. Sibling 6 is 75 years old and was traced to a London hospital where she had been admitted for surgery for AAA. She has glaucoma. Sibling 7 is 72 years old, deaf, but has neither AAA nor glaucoma. Sibling 8 is a patient treated at this hospital. He had AAA, has glaucoma and is deaf. Sibling 9 is 67 years old and has glaucoma and deafness but no AAA. Sibling 10 is 64 years old and within the previous 8 weeks had undergone AAA repair. He has both glaucoma and deafness.

The family's father died aged 54 years from septicaemia and was deaf. The mother died aged 84 years following a stroke. She was blind from glaucoma. There was no consanguinity. Of the next generation (i.e. the children of the family studied), there are as yet no signs of AAA, glaucoma or deafness; the oldest member of this generation is 50 years of age. No previous mention of an AAA-glaucoma-deafness symptom complex can be found in the literature.

Discussion

The incidence of AAA derived from necropsy studies in England and Wales is about 3 per cent in those aged over 50 years¹ and the incidence in the general population appears to be increasing². Dissecting aortic aneurysm in more than one family member (mother and child) was first reported by Griffiths *et al.*³ in 1951; Lawson and Alexander⁴ in 1962 described the condition in two sisters. Non-dissecting AAA in more than one family member was first reported by Clifton⁵ in 1977. He described three brothers with ruptured non-dissecting AAA and suggested a familial basis of inheritance. Tilson and Seashore in 1984 described 50 families with AAA in two or more first-order relatives⁶. Several other reports of familial AAA have since been published (including four cases in identical twins)⁷⁻¹². Familial AAA has been reported in association with various conditions: Marfan's syndrome, Sack's syndrome (vascular Ehlers-Danlos syndrome), cystic medial necrosis, familial haemorrhagic telangiectasia and hereditary polycystic kidney disease¹³⁻²¹.

It has been suggested that a systemic tissue disorder may be the basic pathology in ectatic aortic disease²². In support of this, abnormalities identified in patients with AAA include an irregularity in copper metabolism, deficiency of type III collagen in aortic and skin tissues, and increased skin content of 3-deoxypyridinoline²³⁻²⁷. The relevance of serum lipid levels is less clear; Norrgård *et al.* found a higher concentration of triglyceride and very low density lipoprotein cholesterol, a lower level of high density lipoprotein cholesterol, and a normal total cholesterol level²⁸. Greenhalgh *et al.* found a higher concentration of serum triglyceride and total cholesterol in patients with dilatating arterial disease than in controls²⁹. Brockett-Jones *et al.*, in a pair of twins with AAA, found their serum triglyceride levels to be normal, total cholesterol concentration raised and low density lipoprotein fraction normal¹⁰. Other conditions in which there appears to be an increased incidence of AAA include advanced age (aneurysms are rare before age 50 years)²⁶, male sex (AAA has a male:female ratio of 4-10:1), presence of an aneurysm elsewhere in the body (e.g. popliteal), hypertension (which is present in 67 per cent of cases) and smoking^{8,28}.

Table 1 Summary of patient data

	Sibling no.									
	1	2*	3*	4	5	6	7	8	9	10
Age (years)	83	79	79	79	77	75	72	69	67	64
Sex	M	M	M	F	M	F	M	M	M	M
Abdominal aortic aneurysm	?	+	+	-	?	+	-	+	-	+
Glaucoma	?	+	?	+	+	+	-	+	+	+
Deafness	?	+	?	+	+	-	+	+	+	+

+, Condition present; -, condition absent; ?, unknown; * dead

AAA as an inheritable condition is seen in the blotchy mouse model, in which spontaneous aneurysms develop as a sex-linked trait. In humans, it has been suggested by Tilson and Seashore that the modes of inheritance include both sex linked and autosomal^{6,23,27}. The incidence of AAA in first-degree relatives of affected patients is between three and eight times that in the normal population^{7,8}. Colin *et al.* reported an incidence of 29 per cent in screened male relatives and 5.4 per cent in an unselected male population^{30,31}; Johansen and Koepsell, comparing 250 patients with AAA and 250 controls, found that 19.2 per cent of those with AAA had first-degree relatives with aortic dilatation compared with only 2.4 per cent of the control population. They estimated the risk of AAA among people with affected first-degree relatives to be 11.6 times that in the population at large⁸. Reports therefore have strongly suggested a familial or genetic mode of inheritance in the development of AAA. Other studies have argued that there may be a basic connective tissue abnormality involved which, as well as allowing the development of AAA in later life, may predispose some patients to other mesodermal defects, such as glaucoma and deafness.

Although sibling tracing did not lead to the recognition of any previously undiscovered AAA in the family reported here, the discovery of such a high incidence of AAA lends further credence to the proposal that a familial pattern of inheritance is responsible, at least in part, for the development of this condition. This family exhibits a symptom complex of AAA, glaucoma and deafness, which may reflect an underlying mesodermal disorder.

Acknowledgements

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Selective use of a right retroperitoneal approach to abdominal aortic aneurysm

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The repair of infrarenal abdominal aortic aneurysm by right retroperitoneal dissection using a standard midline transperitoneal incision has previously been described but its clinical application has not been evaluated. Over a 14-year period 144 elective abdominal aortic aneurysm grafts were performed by a single surgical firm. Of these, 11 were carried out by a right retroperitoneal exposure (seven men and four women, aged 63-81 (median 70) years). The indications were to improve access for large juxtarenal aneurysms (n = 6) and because of dense abdominal adhesions (n = 3), horseshoe kidney (n = 1) and retroperitoneal fibrosis (n = 1). In each instance, good proximal control of the aorta was achieved. There were no major operative or postoperative complications and all patients were discharged from hospital (median stay 15 days). Follow-up (median 29 months) has revealed no procedure-related complications.

A standard midline transperitoneal approach generally proves satisfactory for the repair of infrarenal abdominal aortic aneurysm. If the aneurysm is large, access to gain proximal control by the standard approach may prove to be difficult and dangerous. The presence of dense adhesions from previous surgery makes the separation of bowel loops, with the possibility of damage and resultant peritoneal contamination, a major hazard. In an alternative approach in these instances of operative difficulty, suggested by Landvater *et al.*¹ in 1986, a right retroperitoneal dissection follows a transperitoneal approach. A similar approach for selected infrarenal abdominal aortic aneurysms has been used over the past 14 years and this paper reviews the indications and outcome.

Patients and methods

A retrospective analysis of patients undergoing surgery for abdominal aortic aneurysm over a 14-year period was conducted. All 144 elective procedures were carried out through a standard transperitoneal approach, but in 11 a right retroperitoneal dissection was used to expose the great vessels. There were seven men and four women with a median age of 70 (range 63-81) years.

In six patients the right-sided approach was used because of poor access to the neck of the aneurysm by the conventional route. This followed a trial of the conventional approach in four patients; no trial dissection was performed in the other two. Most of these patients had large aneurysms with a median maximal diameter of 8 (range 5-9) cm and a sac that extended to the level of the renal vessels. Three patients had adhesions following previous surgery. One of these presented with recurrent vomiting, which was found on barium meal examination to be due to external compression of the third part of the duodenum by the aneurysm. One patient had a horseshoe kidney, which had been suspected before operation; two lower pole renal arteries arose with a common origin from the anterior wall of the aneurysmal aorta. The final patient presented with abdominal pain and weight loss and the findings of a raised erythrocyte sedimentation rate and a hydro-nephrotic kidney, and was suspected before operation of having retroperitoneal fibrosis. No patient was operated on for an acute rupture but one patient had a localized leak, and surgery was considered to be urgent in three because of abdominal pain or tenderness.

A standard midline laparotomy incision was performed from the xiphisternum to the pubic symphysis with the patient supine on the table. Retroperitoneal dissection commenced by the division of the peritoneal reflection of the right colon and the duodenum (Figure 1). Both were then mobilized to the left until eventually limited by the pedicle of the superior mesenteric vessels. This allowed the full length of the inferior vena cava and the abdominal aorta to be exposed from above the renal vessels to the level of the common iliac arteries (Figure 2). The neck of the aneurysm was encircled by a dissection which started in the angle between the inferior vena cava and the lower

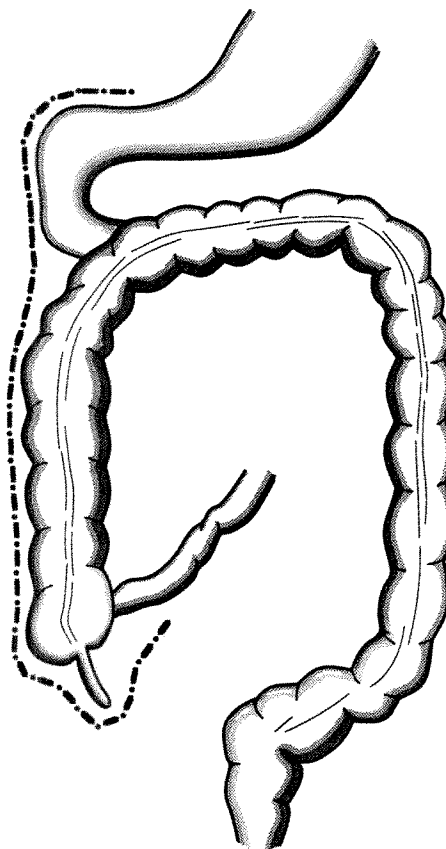


Figure 1 Line of incision for retroperitoneal dissection involving mobilization of the duodenum and right colon

border of the left renal vein, the latter being very clearly seen in this exposure. Where a bifurcation graft was required, the distal dissection was extended to the iliac vessels on both sides.

Results

Satisfactory exposure was obtained and aortic grafting successfully completed in all 11 patients in whom this technique was employed. In the six patients in whom conventional exposure failed, it was possible to gain control of the aneurysm neck under direct vision. In the three patients with adhesions, opening the abdominal cavity did not prove to be a major

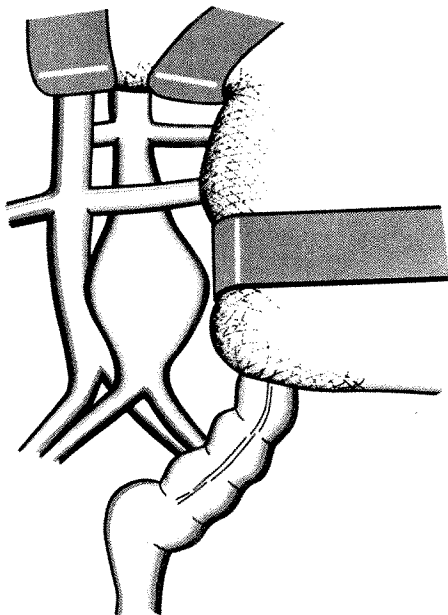


Figure 2 Exposure obtained following the right retroperitoneal dissection. The right colon and small bowel are retracted under the abdominal pack

difficulty but dense adhesions in the preaortic area made this dissection potentially dangerous. The patient with a horseshoe kidney had reimplantation of the lower pole renal arteries into the anterior aspect of the prosthetic graft and preserved normal renal function after operation. The patient with retroperitoneal fibrosis had a thick and dense fibrous plaque over the anterior wall of the aorta which prevented a conventional approach. The right retroperitoneal approach was without major difficulty, although division of the left renal vein was required. After grafting, an omental wrap was performed with a right ureterolysis. At 6 months after operation, the patient had normal serum urea and creatinine levels, and an intravenous pyelogram showed normal excretion from both kidneys.

There were no significant operative or postoperative complications. Six patients had straight grafts inserted and five required bifurcation grafts. Two minor postoperative complications were a transient confusional state in a 71-year-old woman and persistent hypokalaemia in one other case. The median period of hospital stay was 15 (range 11–36) days. The longest stay was in the patient with retroperitoneal fibrosis, who underwent prolonged preoperative investigations. One patient died 5 months after operation from a cerebrovascular accident. All other patients were followed for 6 months to 15 years (median 29 months) and have not developed complications related to aneurysm surgery.

Discussion

This study demonstrates that a right retroperitoneal dissection to expose the abdominal aorta may be successfully employed in cases in which a conventional approach proves to be difficult or impossible. The technique previously described by Landvater and colleagues¹ is similar to that described in this article except that it was not necessary to mobilize the small bowel mesentery and the lower border of the pancreas.

In the present series this procedure was not used for routine infrarenal aneurysms. Other alternatives to this technique are the right and left lateral extraperitoneal approaches^{2–4}. These are associated with a shorter period of postoperative ileus and reduced incidence of respiratory complications compared with the transperitoneal approach⁵. The retroperitoneal approach provides poor access to the contralateral femoral, iliac and renal arteries, and does not allow other abdominal pathology to be detected and dealt with⁶.

The midline approach with right retroperitoneal dissection

may be employed in all patients, provides superb access to the aorta and its branches, and obviates the necessity for preoperative angiography to assess the iliac arteries. As with the conventional approach, however, a significant period of postoperative ileus is encountered.

The combination of an abdominal aortic aneurysm and horseshoe kidney is encountered rarely⁷. The retroperitoneal dissection provided good visualization of the renal vessels and allowed a simple reimplantation of the lower pole vessels.

One of the patients had an aneurysm associated with retroperitoneal fibrosis. The dense layer of fibrous tissue prevented a conventional anterior approach. The retroperitoneal dissection was performed without difficulty. This may be explained by the fibrous thickening surrounding this form of inflammatory aneurysm being non-uniform, the lateral and posterior walls of the aneurysm being less affected by the fibrous reaction⁸. This favours the retroperitoneal approach for this form of aneurysm: the neck of the aneurysm may be approached from the posterolateral wall where fibrosis is minimal^{8,9}. Controlling the neck of the aneurysm from the right side allows an inlay graft to be inserted by incising down the right border of the aneurysm sac without dissecting the thickly fibrosed third and fourth parts of the duodenum from the anterior surface of the aneurysm.

An alternative approach for aneurysms associated with retroperitoneal fibrosis is to clamp the aorta at the diaphragm¹⁰, an area that is relatively spared by the fibrosis⁸, but this produces a period of renal and visceral ischaemia without overcoming the difficulties of access to the neck of the aneurysm.

In conclusion, where a conventional transperitoneal approach to the repair of an abdominal aortic aneurysm proves difficult or impossible, a right retroperitoneal dissection allows satisfactory exposure and should be considered at an early stage.

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Distribution of aortic diameter in a screened male population

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Between September 1990 and August 1991, 2291 men aged 65 years were invited for ultrasonographic screening of the aorta in the Gloucestershire aneurysm screening programme; 1748 (76.3 per cent) attended. An aortic diameter ≤ 2.5 cm was found in 1547 (88.5 per cent); 174 (10.0 per cent) had diameters in the range 2.6–4.0 cm, and 26 (1.5 per cent) had diameters > 4.0 cm. The mean(s.d.) aortic diameter was 2.1(0.55) cm and 97.5 per cent of patients had a diameter ≤ 3.3 cm. Any man over the age of 65 years with an aortic diameter > 3.3 cm has an aortic aneurysm.

In England and Wales approximately 1000 deaths a year can be expected for every 22 000 men aged 65–74 years. Ruptured aortic aneurysm is responsible for 1.3 per cent of these deaths¹. Because aneurysm rupture is frequently not recognized as the cause of death these figures undoubtedly underestimate the severity of the problem². It is estimated that 27–50 per cent of patients with ruptured abdominal aortic aneurysm die before reaching hospital³ and that 42–80 per cent of those who reach the operating theatre die in the perioperative period⁴. The mortality rate for elective surgery is reported in many centres^{5–7} as < 5 per cent.

In recent years the availability of ultrasonography has made diagnosis of aneurysm easier and the number of aneurysms detected has increased. A detailed definition of normality is needed to assist in the elective management of small aneurysms identified by the introduction of screening programmes. When defining aortic aneurysm, two questions regarding dilatation need to be answered: 'A dilatation in comparison with what?' and 'How much dilatation?'. Relatively few patients have a previously documented aortic diameter available for comparison, and the limited information available on aortic diameter in the population shows a progressive increase in both mean diameter and standard deviation with age in both sexes⁸.

With many biological measurements it is customary to regard values within a range 2 s.d. either side of the mean as 'normal' and measurements outside this range as 'abnormal'. The distribution curve of aortic diameter is positively skewed because of aortic aneurysm. If a distribution is skewed, the mean and standard deviation are not good summary measures; medians and percentiles are more appropriate. Both methods were used in the present series to determine a definition for an aneurysm. A previous smaller study has found the incidence of abdominal aortic aneurysm to be 5.4 per cent in the 65–74-year age group⁹.

Ultrasonography is the most useful method for measuring aortic dilatation since it is widely available, cheap, accurate, rapid, reproducible and safe. The main difficulty with computed tomography is that because of tortuosity of the aorta the plane of section may not be at right angles to the long axis of the artery, leading to inaccuracies in the measurement of maximum diameter.

Patients and methods

Between September 1990 and August 1991, 2291 men born in 1925, living in Gloucestershire and appearing in the family practitioner committee records of 77 Gloucestershire practices, were invited for screening. Patients were invited by their general practitioners to attend the surgery for screening by a mobile unit. A preliminary invitation and information letter were sent out before the screening date. Each individual was given a specific appointment and all patients were screened at their own general practitioner's premises during surgery

hours. Patients were seen at 5-min intervals and screening was performed by a senior radiographer. Ultrasonography was carried out using a portable B-mode grey scale machine and 3.5-MHz curvilinear array probe (Aloka SSD 500; Keymed, Southend-on-Sea, UK). Hard copies were made of significant scans using a thermal imager. Aortic measurement was taken from the outer margin of the anterior wall echo to the inner margin of the posterior aortic wall echo and the maximum anteroposterior diameter was recorded after scanning longitudinally. All patients with an aortic diameter ≥ 4.0 cm automatically received an outpatient appointment with a consultant vascular surgeon (B.P.H.) for consideration of elective surgery.

Results

The names and addresses of 2291 men born in 1925 were obtained; 1748 (76.3 per cent) attended. Aortic diameter measurements were made on all but one of those attending and the findings are summarized in Figure 1; in one patient it was not possible to identify the aorta. An anteroposterior aortic diameter > 2.5 cm was found in 200 patients (11.4 per cent); 26 patients (1.5 per cent) had an aortic diameter > 4.0 cm. The mean(s.d.) diameter was 2.1(0.55) cm. The median diameter was 2.0 (range 1.2–7.5) cm. Of the screened population 97.5 per cent had an aortic diameter ≤ 3.3 cm.

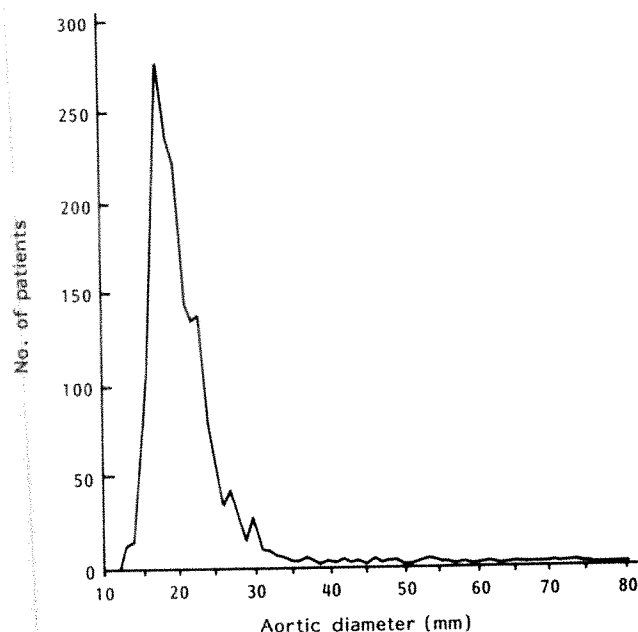


Figure 1 Distribution of ultrasonographically determined aortic diameter in 1747 men aged 65 years

Discussion

The ideal screening programme identifies an abnormality, associated with a significant rate of mortality, that is not otherwise detectable. It should be inexpensive and without side-effects, and treatment should be available that can restore patients to normality. Abdominal aortic aneurysm can rupture without previous symptoms¹⁰ and emergency treatment results in a high mortality rate (30–55 per cent)^{11,12}. Elective surgery, on the other hand, has a low mortality rate (0–5 per cent) and life expectancy after such surgery is similar to that of the rest of the population of the same age¹³. It is worthy of note that 83 per cent of ruptured abdominal aortic aneurysms occur in patients over the age of 65 years¹⁴, and screening of the group aged 65–74 years should detect the majority of treatable aneurysms at risk of rupture. In this study of men aged 65 years, 97.5 per cent of those screened had an aortic diameter of ≤ 3.3 cm.

Smoking and systolic blood pressure >180 mmHg are associated with abdominal aortic aneurysm, but about 50 per cent of aneurysms identified in a pilot study were in either non-smokers or subjects without hypertension. These factors have, therefore, not been used as selection criteria for screening¹⁵.

Having decided that a patient has an aneurysm, selection for treatment is required to avoid unnecessary surgery, because two-thirds of patients with abdominal aortic aneurysm do not die from rupture. Selection should be made on the basis of fitness for surgery, aneurysm size and expansion rate, and symptoms. The behaviour of aortas with diameters between 2.6 and 4.0 cm has been shown to be unpredictable¹⁶ and there are obvious financial implications for screening programmes if approximately 12 per cent of the screened population may require regular re-examination possibly for 5 years or more. It is our present policy, based on these and previous results, to follow up patients with an aortic diameter >2.5 cm with ultrasonographic scans at 1-year intervals and to refer those with a diameter of ≥ 4.0 cm for further surgical assessment. There has been no study to date on the natural history of aortas <2.5 cm in diameter at 65 years, but this information will be available from future results of the screening programme.

This study shows that an aortic diameter >3.3 cm is statistically abnormal. Further follow-up of these patients will determine whether aortas between 2.6 and 3.3 cm merely represent the upper end of a normal range or are aneurysms in the making.

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Thoracoscopic enucleation of leiomyoma of the oesophagus

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Case report

A 48-year-old woman presented with a 3-year history of epigastric discomfort and heartburn, and 6 months of dysphagia for solids with retrosternal pain. She had lost 4 kg in weight. Barium swallow showed the typical features of a mid-oesophageal leiomyoma. On oesophagoscopy a 2-cm mass covered by normal mucosa was noted at 25 cm in the right posterior oesophagus. The leiomyoma was removed using a transthoracic endoscopic technique, which is described.

Surgical technique

The operation was performed under general anaesthesia, with the patient in the left lateral position. A double-lumen endotracheal tube was used and the right lung was collapsed. Carbon dioxide insufflation was not required and the valves were removed from the standard operating cannulae to facilitate instrumentation. Seven thoracic stab incisions were made for instrumentation (Figure 1). The operating camera was inserted through a 10-mm cannula, and the right lung retracted medially using two 5-mm rods. The tumour was situated medial to the azygos vein in the posterior oesophageal wall, and its position confirmed by transillumination with a flexible endoscope. The azygos vein was divided between no. 1 catgut and locking polydioxanone clips (Absolok; Ethicon, Edinburgh, UK). Dissecting forceps and a hook diathermy, both inserted through 5-mm cannulae, were used to mobilize about 10 cm of the oesophagus (Figure 2). The oesophagus, which was suspended from a sling that had been inserted and recovered through a 5-mm cannula, was rotated to allow a longitudinal myotomy to be made over the lesion with diathermy. The encapsulated tumour was enucleated intact and removed through a 20-mm cannula. The oesophageal mucosa was confirmed to be intact by endoluminal endoscopy. The muscularis propria was repaired with 4/0 catgut. A 40-Fr chest drain was inserted and the wounds closed. The patient made an uneventful recovery and dysphagia was reduced. Histological examination confirmed the lesion to be a leiomyoma.

Discussion

Oesophageal leiomyoma is an uncommon benign tumour of smooth muscle origin. Malignant transformation is rare, but removal is often required on symptomatic grounds. Thoracoscopic resection offers distinct advantages for the treatment of such lesions but may not be applicable to the 10 per cent of patients requiring oesophageal resection¹. Thoracoscopic resection is less invasive than open surgery, avoids the scar and discomfort of thoracotomy, and problems such as atelectasis are likely to be less common. The requirement for analgesia after operation should be considerably less. The procedure should be associated with low morbidity and mortality rates. Thoracoscopic enucleation preserves the capsule of the tumour, whereas diathermy, laser and sclerosing methods breach this boundary, predisposing to local recurrence. Intraluminal ablation^{2,3} is associated with destruction and scarring of the mucosa and the risk of oesophagopleural fistulation. Should endoluminal ablation prove impossible, or perforation or major haemorrhage occur, then an open approach will be necessary. These risks exist for thoracoscopic enucleation, but in this

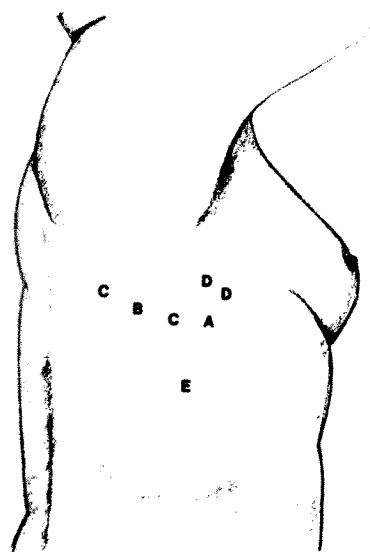


Figure 1 Seven stab incisions were required. A, 20-mm cannula for removal of tumour; B, 10-mm cannula for operating camera; C, two 5-mm cannulae for operating instruments (forceps and hook diathermy); D, two 5-mm rods for lung retraction; E, sling exit site

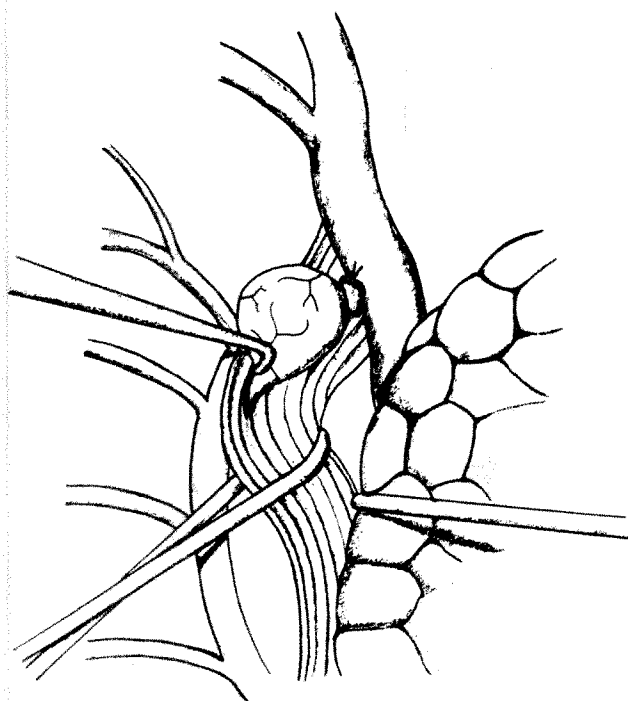


Figure 2 The mobilized oesophagus was incorporated in a sling after division of the azygos vein. The lesion was enucleated through a longitudinal myotomy

instance the patient will already be suitably positioned and anaesthetized for immediate thoracotomy.

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Delayed surgery for congenital diaphragmatic hernia

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Between January 1987 and December 1990, 67 neonates were treated for congenital diaphragmatic hernia, symptomatic within 6 h of birth. The mortality rate was 33 per cent. Preoperative stabilization was achieved in 47 patients, all of whom survived initial treatment, although two died later. Stabilization could not be achieved in 20 neonates, all of whom died within 3 days of birth, 18 without undergoing operation and two after early repair. Intensive resuscitation with controlled, delayed operation for congenital diaphragmatic hernia gives long-term results similar to those of urgent operative repair. This approach avoids operation in the majority of those who subsequently die.

Before 1986, all neonates presenting to this unit with congenital diaphragmatic hernia underwent urgent operative repair¹⁻³. During 1986 this strategy of management was revised to one of preoperative stabilization followed by delayed operation. This report seeks to assess the efficacy of this modification.

Patients and methods

Between January 1987 and December 1990, 67 consecutive neonates (48 boys, 19 girls) were treated for congenital diaphragmatic hernia, symptomatic within the first 6 h of life. Surgeons agreed on a basic strategy of delaying operation until adequate stabilization of the circulation and gaseous exchange had been achieved.

The duration of gestation was >36 weeks in 62 infants but two each were born at 35 and 33 weeks and one at 31 weeks. Birth-weights ranged from 1.4 kg (one infant) to >2.5 kg (55 infants), with 11 weighing 1.5-2.5 kg. Diagnosis was made before birth in nine patients, three of whom died.

All but four patients underwent intubation and ventilation at the referring hospital. Chest and abdominal radiographs were obtained on arrival at the surgical unit; preductal arterial blood gas estimations were performed and ventilator settings adjusted accordingly. All

ventilated infants were paralysed with vecuronium and received infusions of fentanyl or morphine. Bowel decompression was achieved by nasogastric aspiration.

Intravascular volume was maintained with intravenous infusions of 4.5 per cent human albumin in aliquots of 10 ml per kg body-weight and persistent hypotension was treated with dopamine infusion (5-20 µg/kg/min). The response was monitored by measuring the blood pressure, the peripheral-core temperature difference and the urine output. When the above measures combined with maximal ventilation failed to control hypercapnic acidosis, an intravenous bolus of 2 mg/kg tolazoline was given and, if a satisfactory response was achieved, this was followed by infusion^{2,3} at 2 mg/kg/h.

In all but two infants, operation was delayed until there was haemodynamic stability, acidosis was corrected, adequate gaseous exchange had been achieved and the infant 'weaned off' vasodilatory drugs. One infant required preoperative haemofiltration for 48 h before satisfactory excretion of urine was achieved.

All operations were performed through a transverse, upper abdominal incision. Primary sutured repair of the diaphragm was carried out in most but a prosthetic patch of woven Dacron velour (Polyester; Du Pont, Stevenage, UK) was used whenever primary repair without tension could not be achieved. All infants underwent postoperative ventilation as a matter of policy.

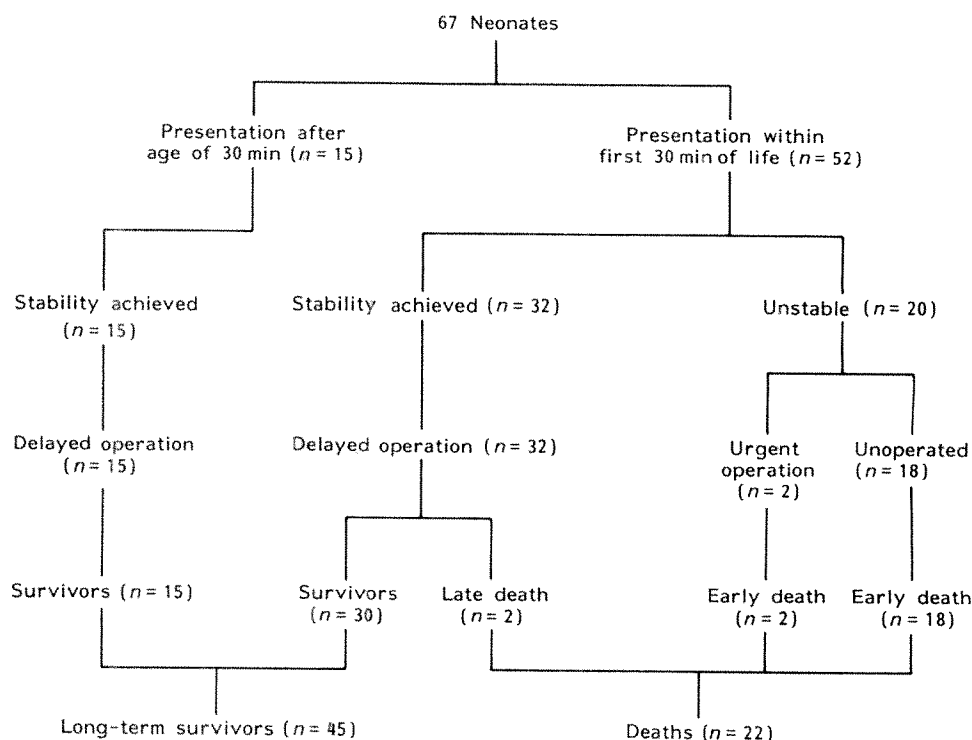


Figure 1 Progress of 67 neonates with congenital diaphragmatic hernia

Results

The progress of the patients is demonstrated in Figure 1. The overall mortality rate was 22 of 67 (33 per cent). Death occurred before operation in 18 infants (27 per cent). Operative repair of the diaphragmatic hernia was performed during the first day of life for seven infants (two of whom died a few hours later), during the second to fifth day of life in 38 (of whom two later died) and after the fifth day of life in four patients, all of whom survived.

Right-sided hernias were less common than those on the left, but were associated with a significantly higher mortality rate (χ^2 with Yates' correction 8.64, 1 d.f., $P < 0.01$) (Table 1). None of the 33 infants who underwent primary sutured repair died, whereas death occurred in four of the 16 with large defects requiring a prosthetic patch. No deaths occurred in the 15 neonates who developed respiratory distress after the age of 30 min.

Of the 52 infants who developed symptoms within 30 min of birth, 22 (42 per cent) died: 18 before and four after operation. Death occurred during the first day of life in 14 infants and during the second or third days in six. One prematurely born infant died from chronic respiratory failure during the seventh month of life and another died at the age

Table 1 Outcome in relation to the side of diaphragmatic hernia

	No.*	Survivors†
Left	50 (75)	39 (78)
Right	17 (25)	6 (35)
Total	67 (100)	45 (67)

Values in parentheses are percentages of: *column totals; †row totals

Table 2 Mortality rate related to the use of artificial ventilation, inotropic (dopamine) and vasodilatory (tolazoline) support in 52 infants who developed symptoms within 30 min of birth

Group	Treatment	No.	Deaths
1	Adequate preoperative ventilation without pharmacological support	13	0 (0)
2	Adequate preoperative ventilation with response to tolazoline alone	1	0 (0)
3	Adequate preoperative ventilation with dopamine alone	9	1 (11)*
4	Difficulty with preoperative ventilation and dopamine, but some response to tolazoline	11	3 (27)*†
5	Failure of stabilization and no response to ventilation, dopamine and either tolazoline ($n = 15$) or prostacyclin ($n = 3$). Death without operation	18	18 (100)
Total		52	22 (42)

Values in parentheses are percentages. *One late death occurred after satisfactory preoperative stabilization; †two patients underwent operation without preoperative stabilization

Table 3 Duration of postoperative ventilation in 47 infants stabilized before operation

Duration of postoperative ventilation (weeks)	No.	Deaths
<1	25	0
1-4	17	0
>4	5	2*
Total	47	2*

*Two late deaths at 3 and 7 months

of 3 months from a combination of respiratory failure, convulsions and severe enteropathy (both had undergone prosthetic patch repair of the diaphragm). No deaths occurred among the 13 infants not requiring pharmacological support (Table 2) but 21 of the 29 (72 per cent) who received both dopamine and a vasodilatory drug died. Of the 30 who received a vasodilator, 12 demonstrated at least a temporary response, of whom nine underwent successful operative repair; one died 7 months after operation, and two died soon after operation without achieving preoperative stabilization. No response to the drug was obtained in 18 infants, who all died without undergoing operation.

The duration of postoperative ventilation for the 47 infants stabilized before operation is recorded in Table 3. Peak inspiratory pressures exceeding 30 cmH₂O were required by 27 infants, eight of whom survived with bronchopulmonary dysplasia. Five of these eight required ventilation for > 1 month.

Discussion

Between 1980 and 1986, 42 per cent of patients with congenital diaphragmatic hernia which presented within 30 min of birth died after early operation¹. The possible advantages of delaying operation until circulatory stability and adequate gaseous exchange had been achieved in these infants, as suggested by reports from other centres⁴⁻⁶, was subsequently considered. This study reports the findings with this new policy.

The rationale for this approach is that congenital herniation of the abdominal viscera into the chest is rarely an acute event causing pulmonary compression, but rather an anomaly developing early in fetal life that is associated with pulmonary hypoplasia. The major cause of death is respiratory insufficiency secondary to severe pulmonary hypoplasia and/or pulmonary hypertension. Early operative reduction of the hernia rarely results in immediate improvement in gaseous exchange⁷ and some infants enjoy a brief postoperative 'honeymoon' period with satisfactory blood gas levels, but then go into a state of rapid, often irreversible, decline with right-to-left shunting of deoxygenated blood secondary to persistent pulmonary hypertension. Repair of the hernia under tension may reduce pulmonary compliance and, by 'splinting' the diaphragm and restricting chest expansion, may hinder mechanical ventilation and increase circulatory instability^{8,9}. Preoperative ischaemia of the herniated viscera is a rare event and, provided the infant is kept paralysed and mechanically ventilated, the gastrointestinal tract can be decompressed by nasogastric tube aspiration in most cases, obviating the need for emergency operation.

The overall mortality rate for both the 1980-1986 patients¹ and the present series was 33 per cent but the preoperative mortality rate increased from 4 to 27 per cent and the early postoperative rate fell from 29 to 3 per cent. Only nine patients in the present series were diagnosed before birth. There is a trend towards the delivery of affected fetuses in units offering on-site neonatal surgical and obstetric care because the prognosis for patients diagnosed before birth is said to be poor^{5,10}. In this series, however, the incidence of death for those diagnosed before or after birth was the same.

The majority (86 per cent) of operations were performed after 24 h of age with only two late deaths. The planned delay between diagnosis and operative repair allows intensive resuscitation to achieve cardiovascular stability with adequate ventilatory exchange and renal function. One feature of this approach is the eradication of the phenomenon of the postoperative 'honeymoon' period. Increased concentrations of prostanooids and other vasoactive metabolites of arachidonic acid have been correlated with persistent pulmonary hypertension¹¹ and raised concentrations of circulating prostanooids have been reported by Bos *et al.*¹² in neonates undergoing repair of diaphragmatic hernia. They suggested that this is an argument in favour of delaying operation until stability has

been achieved. None of our infants stabilized before operation developed increasing right-to-left shunting that required postoperative administration of pulmonary vasodilatory drugs. In contrast, four patients required >5 days of intensive supportive treatment to achieve a stable cardiorespiratory state.

Renal failure may occur in neonates with diaphragmatic hernia^{1,13}. This was a common terminal event in patients who could not be stabilized, but only one stable infant developed renal failure; this responded to preoperative haemofiltration. There were no cases of postoperative renal failure in the stabilized group.

Some authors have stressed the importance of inotropic support for these neonates¹⁴. Dopamine improves peripheral and renal perfusion, thereby reducing acidosis. Of the 38 infants receiving dopamine in this series only 16 survived. In our experience the value of dopamine is to maintain an adequate perfusion pressure, particularly in infants receiving tolazoline, which acts as a pulmonary and peripheral vasodilator.

There has been a marked increase in the number of patients repaired with a prosthetic patch. Of the 49 infants undergoing operative repair in the present series, 16 (33 per cent) had a patched repair (with 14 early survivors) whereas in the whole of the 1980–1986 series¹ only 13 of the 114 patients (11 per cent) had a patched repair (with two survivors). In the past, a prosthesis was used only when primary repair was impossible, but patches are now used when primary suture would create tension in the repaired diaphragm. In this situation, a patched repair results in an improved, dome-like contour of the diaphragm, which is reputed to reduce intra-abdominal pressure and so facilitate postoperative ventilation and renal perfusion^{15–17}.

The selective use of extracorporeal membrane oxygenation (ECMO) may have a limited role in improving survival in some infants^{18,19}, but 64 per cent of deaths in this series occurred during the first 24 h of life. As there are administrative problems inherent in rapidly establishing these infants on ECMO, 12 of the 18 in group 5 (Table 2) might have been effectively excluded from an ECMO programme⁵. Ideally ECMO would be available for patients requiring high-pressure ventilation who had demonstrated a positive response to tolazoline, suggesting that they had transient pulmonary hypertension rather than irreversible pulmonary hypoplasia; only the two patients who could not be stabilized in group 4 (Table 2) would have been ideal candidates for ECMO. As ECMO may have a role in reducing barotrauma in survivors requiring high-pressure ventilation, a further three infants may have benefited from postoperative ECMO, making a maximum of 11 potential beneficiaries (i.e. three patients per year).

The experience reported here indicates that the long-term survival rate after controlled delayed operation following adequate preoperative stabilization is similar to that after urgent operative repair. The successful outcome in all but two of the 47 stabilized neonates commends this form of management of congenital diaphragmatic hernia presenting at birth. Although the operation may be delayed, it is important to note that intensive resuscitation must begin immediately after birth to ensure a successful outcome.

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Mirizzi syndrome managed by endoscopic stenting and laparoscopic cholecystectomy

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Mirizzi syndrome type II is an uncommon obstructive jaundice caused by external compression of the common hepatic duct by gallstones and formation of a cholecystocholedochal fistula^{1,2}. Most patients are elderly and frail. Preoperative diagnosis and careful surgical management are essential in avoiding bile duct injury^{3,4}. This paper describes successful treatment by endoscopic biliary stenting and laparoscopic subtotal cholecystectomy.

Case report

An 81-year-old man presented with acute cholecystitis and obstructive jaundice. Ultrasonographic examination confirmed gallstones and dilatation of the biliary system. Endoscopic retrograde cholangiopancreatography (ERCP) (Figure 1) showed appearances of type II Mirizzi syndrome.

The patient suffered from depression, pulmonary fibrosis, ischaemic heart disease and peripheral vascular disease. He was considered unfit for major surgery and was referred for endoscopic biliary drainage. A Wilson-Cook stent (14 cm, 12 Fr) was inserted. Jaundice improved but toxemia persisted despite antibiotic treatment. Laparoscopic cholecystectomy was performed 48 h later.

The pneumoperitoneum was established and four cannulae were inserted. The gallbladder was inflamed and packed with stones. There were few adhesions to the gallbladder itself, but the common bile duct (CBD) and cystic duct were obliterated by dense fibrous tissue, making dissection in this area hazardous. Retrograde diathermy hook dissection was performed from the fundus to Hartmann's pouch and the gallbladder was divided at this level. Stones impacted in Hartmann's pouch were dislodged by blunt dissection revealing the fistula into the



Figure 1 Extrinsic compression of the common hepatic duct caused by gallstones in Hartmann's pouch

CBD through which the stent was clearly visible. A T tube drain was placed into the fistula. Suction drains were positioned in the subhepatic and subphrenic spaces. The gallbladder and stone debris were removed. Copious saline lavage was performed.

There was some initial bile drainage which ceased when the T tube was removed. The patient's recovery was delayed by cardiac arrhythmia, cardiac failure, respiratory failure and an exacerbation of his depressive illness, all of which responded to appropriate medical therapy. He was discharged on the 19th day after operation. ERCP and stent removal were performed 6 weeks later without complication.

Discussion

P. L. Mirizzi described a syndrome of obstructive jaundice from gallstones impacted in the cystic duct or Hartmann's pouch causing extrinsic compression of the common hepatic duct. Many surgical approaches of varying complexity have been advocated for treating this syndrome.

Immediate surgery despite jaundice has been recommended³, but other workers suggest initial nasobiliary drainage⁴. Total cholecystectomy involves a high risk of bile duct injury² because of the obliteration of Calot's triangle and anomalous anatomy with a predominance of a low insertion of the cystic duct⁵. Subtotal retrograde cholecystectomy may reduce the risk of bile duct injury^{3,4}. Laparoscopic cholecystectomy lends itself well to fundus-first dissection and gives excellent anatomical views.

Dewar⁴ described T tube drainage of the common hepatic duct via the fistula, while Baer *et al.*³ recommended a biliary-enteric bypass, having abandoned previous attempts simply to close the fistula. The present authors placed a modified T tube in the common hepatic duct, but this merely encouraged leakage of bile from the fistula, prevented normal function of the stent and delayed natural closure of the fistula.

Jaundice and acute inflammation are considered by some to be contraindications to laparoscopic surgery⁶. Percutaneous cholecystostomy or cholecystolithotomy might have been considered but we have no expertise in these procedures. Preoperative ERCP with stenting gave excellent appreciation of the anatomy and improved the jaundice if not the cholecystitis. We doubt that open operation would have been safer, particularly as we have considerable experience in endoscopic stenting and laparoscopic cholecystectomy. We therefore recommend this minimally invasive approach when appropriate endoscopic and surgical expertise is available.

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Effect of biliary decompression on reticuloendothelial function in jaundiced rats

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The recovery of reticuloendothelial system (RES) function following decompression of obstructive jaundice was studied using a rat model with bile duct ligation and side-to-side choledochoduodenostomy. Histopathological changes in the liver were still present 5 weeks after relief of jaundice, while results of liver function tests had returned to normal. RES function evaluated by the blood clearance and organ uptake of radiolabelled Escherichia coli using a corrected phagocytic index gradually returned to normal following biliary decompression. The severely impaired RES activity noted 1 week after operation may explain the increased incidence of sepsis and renal insufficiency in the early period after biliary surgery in jaundiced patients.

Patients with obstructive jaundice have an increased incidence of sepsis¹ and renal impairment^{2,3} after surgery. A number of experimental studies have demonstrated a depression of the reticuloendothelial system (RES) following biliary obstruction^{4,5}. The relief of jaundice has been considered important to decrease these complications. Experimental models of biliary decompression have been developed for studying biochemical, histological and immunological changes⁶⁻⁸, but the pathophysiological changes in RES function in jaundiced animals and after biliary decompression remain to be understood. The present study was designed to establish a model of choledochoduodenostomy in the jaundiced rat and to assess RES function after the relief of jaundice.

Materials and methods

Animals and experimental design

Male Sprague-Dawley rats (Anticimex, Stockholm, Sweden) of mean (s.e.m.) weight 401 (6) g were randomized to seven groups of six rats each. They were housed under controlled temperature, humidity and lighting (12-h light-dark cycle) and allowed tap water and rat pellets (R34; Ewos-ALAB, Södertälje, Sweden) *ad libitum* before and after operation. The experimental design is shown in Figure 1. Group 1 (controls) received common bile duct (CBD) mobilization without ligation and division, whereas group 2 rats underwent CBD ligation and transection. Animals in groups 3 and 5-7 were also subjected to CBD ligation and transection and to biliary decompression, 2 weeks after CBD ligation, followed by evaluation of liver and RES function after an additional 1 week (group 3), 2 weeks (group 5), 3 weeks (group 6) and 5 weeks (group 7). Group 4 rats were studied 1 week after sham biliary decompression, also 2 weeks after CBD ligation. Another group of four rats was used for serial studies of changes in liver function and patency of the anastomosis. Blood clearance and organ distribution of ¹²⁵I-radiolabelled *Escherichia coli*, histological examination and liver function tests were carried out in all animals.

Surgical models

A 1.5-cm upper midline abdominal incision was made, through which the CBD was identified, ligated twice with 5/0 silk and divided. After 2 weeks, a 4-cm upper midline abdominal incision was performed. The proximal CBD was dilated in all animals and none was patent. Choledochoduodenostomy was performed to achieve biliary decompression. Both the dilated CBD remnant and the duodenum were incised longitudinally for about 0.8 cm. A side-to-side anastomosis was established by a continuous single-layer suture using 6/0 silk. All operations were performed using ether anaesthesia under clean but not sterile conditions.

Radiolabelling of *E. coli*

The method has been described in detail previously⁹. *E. coli*, serotype 046:K1:H31, was isolated from a patient's abscess and cultured in Todd-Hewitt broth overnight at 37°C, heat-killed at 80°C for 30 min

and washed three times in phosphate-buffered saline (0.03 M phosphate, 0.12 M saline, pH 7.2; Sigma, St Louis, Missouri, USA), and then suspended in phosphate-buffered saline. Bacteria were labelled with ¹²⁵I using the protein-labelling method of McConahey and Dixon¹⁰. After labelling and three additional washes in phosphate-buffered saline and centrifugation (1700 r.p.m. for 10 min), the suspension was frozen at -20°C and thawed immediately before use. The radioactivity was about 2 × 10⁷ c.p.m. per ml bacterial suspension.

Blood clearance and organ uptake of radiolabelled *E. coli*

The blood clearance study of radiolabelled *E. coli* was carried out at 1, 2, 3 and 5 weeks after biliary decompression and 2 weeks after CBD ligation in the CBD ligation group. In controls, the study was performed 2 weeks after sham laparotomy at which the CBD was mobilized but not ligated. Group 4 (CBD ligation and 1 week sham biliary decompression) was used as a control of group 3 (1 week biliary decompression). Catheters were inserted into the femoral artery (outer diameter 0.75 mm; Portex, Hythe, Kent, England) and vein (outer diameter 0.94 mm; Dow Corning, Michigan, USA), respectively. An aliquot of 2 × 10⁶ c.p.m. (100 µl) ¹²⁵I-radiolabelled *E. coli* was injected intravenously. Arterial blood samples (500 µl) were taken immediately before intravenous challenge (for liver function tests) and 2, 8 and 15 min after injection (for blood clearance of radiolabelled *E. coli*). The liver, spleen, lungs and kidneys were removed after killing the animal by exsanguination immediately after the 15-min sample. The organs were rinsed in physiological saline, blotted in gauze and weighed. A constant segment of each organ was removed for measurement of radioactive uptake. Liver and kidney specimens were sent for histopathological examination. A 150-µl sample of blood was used for determination of radioactivity, which was measured using a γ-counter (1272 Clinigamma; LKB, Wallac, Finland) and expressed as ¹²⁵I c.p.m. ml⁻¹ (blood samples) and c.p.m. g⁻¹ (organ samples), respectively. The elimination rate constants in blood were calculated using the method of least squares and expressed as mean (s.e.m.).

RES activity was estimated by the phagocytic index (*k*), which is the slope of the blood disappearance curve of the radiolabelled *E. coli*. The corrected phagocytic index (*α*), calculated from the equation below^{4,11}, renders possible a comparison between animals with different organ weights and between different species.

$$\alpha = \frac{\text{Total body-weight}}{\text{Combined weight of liver and spleen}} \times k^{1/3}$$

Imaging examination

Postoperative cholangiography was performed 5 weeks after biliary decompression under ether anaesthesia. An upper midline abdominal incision was made. A purse-string suture was applied on the dilated remnant CBD where a needle puncture was performed in the centre of the suture and bile was aspirated. A silicone catheter (outer diameter 0.94 mm; Dow Corning) was inserted into the CBD through the puncture site and tied. Radiograms were taken after injection of 2 ml contrast medium (Isopaque, Cerebral 280 mg l ml⁻¹; Nyegaard, Oslo, Norway). Methylene blue was then injected into the bile duct.

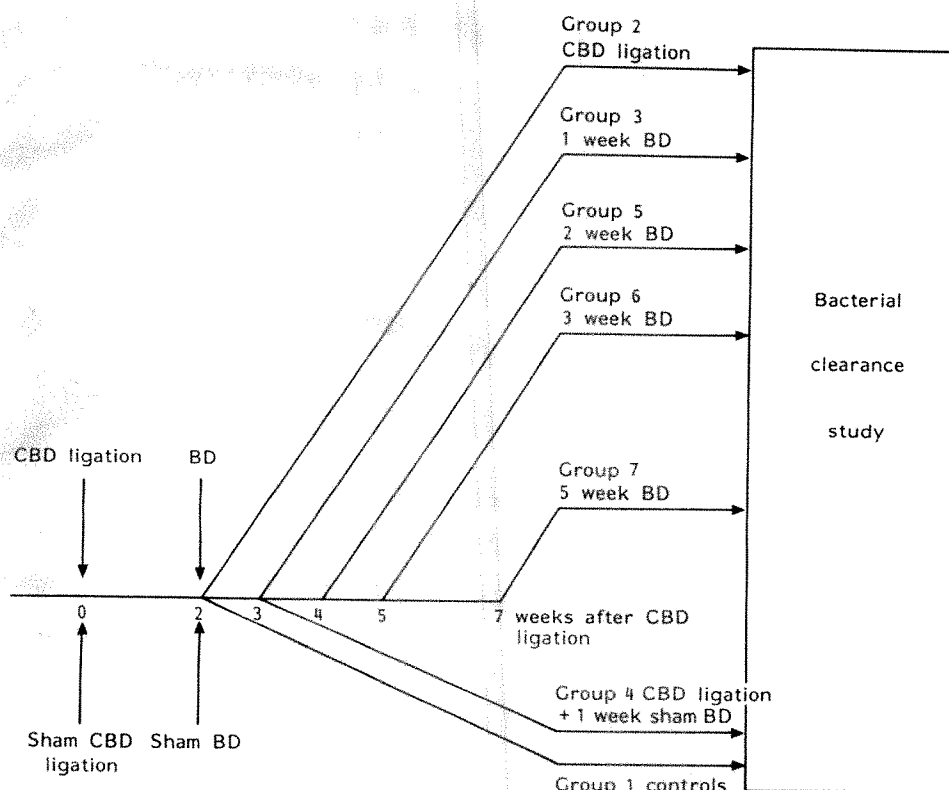


Figure 1 Experimental design. CBD, common bile duct; BD, biliary decompression

Table 1 Ratios of organ weights to body-weight

Group		Liver	Spleen	Lungs	Kidney
1	Controls	0.040(0.002)	0.0021(0.00008)	0.0013(0.00004)	0.0036(0.0001)
2	CBD ligation	0.050(0.001)†	0.0036(0.00008)†	0.0046(0.0003)†	0.0040(0.0001)*
3	1 week BD	0.047(0.002)*	0.0049(0.0006)†	0.0052(0.0007)†	0.0041(0.0001)*
4	CBD ligation + 1 week sham BD	0.066(0.003)†	0.0050(0.0010)†	—	—
5	2 week BD	0.040(0.002)	0.0029(0.0002)*	0.0051(0.0002)†	0.0036(0.0001)
6	3 week BD	0.038(0.0012)	0.0028(0.0002)*	0.0040(0.00016)†	0.0037(0.00013)
7	5 week BD	0.037(0.0006)	0.0025(0.0001)*	0.0049(0.0001)†	0.0034(0.00002)

Values are mean(s.e.m.). CBD, common bile duct; BD, biliary decompression. * $P < 0.05$; † $P < 0.001$ (all versus controls, ANOVA)

Histopathological study

Liver and kidney specimens were fixed in formalin, embedded in paraffin, stained with haematoxylin and eosin and examined under the light microscope.

Statistical analysis

One-way analysis of variance (ANOVA) was used for statistical analysis. A probability level of $P < 0.05$ was considered as statistically significant. Values are expressed as mean(s.e.m.).

Results

Bilirubin was noted in the urine after CBD ligation. Extrahepatic biliary obstruction also resulted in markedly raised serum levels of bilirubin and dilatation of the proximal remnant of the CBD. The anastomotic width was measured to be about 0.6 cm 5 weeks after biliary decompression.

Body-weight and organ weights

The body-weights of rats in groups 2–5 remained almost unchanged, whereas they increased in controls 2 weeks following CBD ligation or sham operation, respectively. Animals in groups 6–7 gained weight with time after biliary decompression. Table 1 shows the organ weight:body-weight ratios at the end of the experiments. The hepatic and splenic

ratios were significantly higher in the CBD ligation group and group 4 when compared with both controls and all the other groups, except for group 3 (1 week after biliary decompression). No significant differences were found between groups 5, 6 and 7.

Blood clearance and organ localization of bacteria

The corrected phagocytic index (α) in groups 2–5 was significantly lower ($P < 0.001$) compared with controls, while no difference was seen between controls and groups 6 and 7 ($P > 0.05$), with 3 and 5 weeks' biliary decompression (Figure 2).

Table 2 shows the organ uptake of radiolabelled *E. coli*. Hepatic localization of ^{125}I -radiolabelled *E. coli* in all experimental groups was significantly higher ($P < 0.05$) compared with controls. Splenic uptake of labelled *E. coli* was significantly higher ($P < 0.01$) in groups 6 and 7 compared with controls.

Renal uptake of radiolabelled *E. coli* in the CBD ligation group and groups 3 and 4 was significantly higher ($P < 0.05$) compared with controls, and higher, though not significantly so, than in the remaining experimental groups. The pulmonary uptake of radiolabelled *E. coli* in group 4 was significantly higher than in all the other experimental groups.

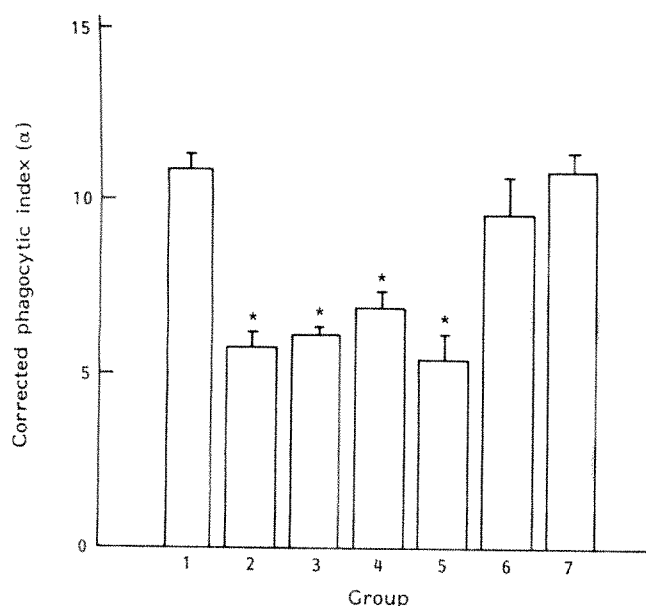


Figure 2 Mean (s.e.m.) corrected phagocytic index (α) in the various groups. * $P < 0.001$ (groups 2–5 versus controls (group 1), ANOVA)

Liver function tests

The serum bilirubin ($P < 0.001$), alanine aminotransferase, asparagine aminotransferase and alkaline phosphatase ($P < 0.01$) levels 2 weeks after CBD ligation in the various groups were significantly raised when compared with the corresponding levels before CBD ligation. Results of liver function tests, however, dramatically decreased ($P < 0.01$) following biliary decompression and rapidly regained baseline levels, whereas liver function test data still remained as high as at 2 weeks of CBD ligation following sham biliary decompression (group 4). No differences in results of standard liver function tests between the groups could be seen at the various intervals following biliary decompression except for levels of bilirubin (Table 3). In the additional group of four rats, serum bilirubin, asparagine aminotransferase and alkaline phosphatase levels were also markedly raised following 2 weeks' biliary obstruction. One week after biliary decompression, they returned to normal levels (Figure 3).

Radiological study

The CBD and small intestine were visualized immediately after injection of contrast medium. The duodenum was stained blue immediately after injection of methylene blue into the catheter placed in the CBD. Thus, both examinations showed the

Table 2 Organ uptake of radiolabelled *Escherichia coli*

Group		Liver (c.p.m. g ⁻¹)	Spleen (c.p.m. g ⁻¹)	Lungs (c.p.m. g ⁻¹)	Kidney (c.p.m. g ⁻¹)
1	Controls	22 436(2823)	27 935(2565)	14 792(4679)	1526(111)
2	CBD ligation	43 787(6121)*	30 846(3301)	11 520(1620)	2225(212)*
3	1 week BD	53 156(3208)‡	28 855(4288)	10 739(1599)	2111(112)*
4	CBD ligation + 1 week sham BD	55 746(3157)‡	29 297(2347)	18 276(1658)	2084(213)*
5	2 week BD	50 743(5583)†	31 660(5554)	9038(2697)	1785(307)
6	3 week BD	55 302(3912)‡	50 605(4319)†	9230(1018)	1888(105)
7	5 week BD	50 613(836)‡	61 862(6802)†	8053(1145)	1811(102)

Values are mean (s.e.m.). CBD, common bile duct; BD, biliary decompression. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ (all versus controls, ANOVA)

Table 3 Results of liver function tests

Group		Bilirubin ($\mu\text{mol l}^{-1}$)	ALAT ($\mu\text{kat l}^{-1}$)	ASAT ($\mu\text{kat l}^{-1}$)	AP ($\mu\text{kat l}^{-1}$)
Before CBD ligation					
1	Controls	4.67(0.82)	1.11(0.15)	2.47(0.71)	9.53(1.88)
2	CBD ligation	2.68(0.47)	0.87(0.05)	1.37(0.04)	8.43(0.54)
3	1 week BD	4.83(0.60)	1.09(0.15)	2.53(0.49)	9.03(1.10)
4	CBD ligation + 1 week sham BD	2.40(0.45)	1.00(0.09)	2.03(0.38)	6.95(1.25)
5	2 week BD	4.85(1.37)	1.10(0.10)	1.70(0.18)	7.41(0.56)
6	3 week BD	5.13(0.88)	1.11(0.12)	1.38(0.14)	8.65(0.45)
7	5 week BD	5.00(0.63)	1.06(0.13)	1.78(0.07)	7.33(0.28)
After CBD ligation					
1	Controls	5.83(1.72)	1.21(0.21)	2.73(0.95)	9.38(3.44)
2	CBD ligation	129.83(6.96)‡	1.19(0.18)	3.01(0.49)	13.37(0.94)‡
3	1 week BD	104.83(13.19)‡	2.37(0.57)	4.11(0.68)*	18.33(1.30)‡
4	CBD ligation + 1 week sham BD	98.67(8.05)‡	4.23(0.57)†	6.87(1.16)‡	20.75(3.47)†
5	2 week BD	117.92(20.20)‡	2.20(0.07)‡	5.18(0.42)‡	17.98(0.30)‡
6	3 week BD	135.97(8.53)‡	2.27(0.24)†	5.74(0.72)‡	17.75(0.72)‡
7	5 week BD	176.50(19.30)‡	1.71(0.18)†	4.83(0.75)†	21.00(1.88)‡
After BD/sham BD					
3	1 week BD	10.00(0.85)	1.00(0.08)	1.68(0.20)	8.38(0.99)
4	CBD ligation + 1 week sham BD	122.67(7.60)‡	1.21(0.12)	4.05(0.35)†	26.20(1.04)‡
5	2 week BD	2.87(1.10)	0.84(0.05)	1.58(0.29)	9.05(1.18)
6	3 week BD	1.80(0.06)	0.66(0.14)	1.17(0.08)	7.45(0.07)
7	5 week BD	1.85(0.06)	1.09(0.05)	1.31(0.09)	6.25(6.25)

Values are mean (s.e.m.). CBD, common bile duct; BD, biliary decompression; ALAT, alanine aminotransferase; ASAT, asparagine aminotransferase; AP, alkaline phosphatase. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ (versus both controls and levels before CBD ligation, ANOVA)

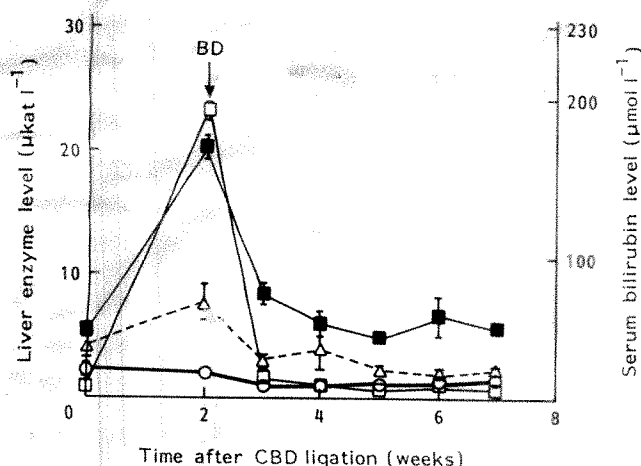


Figure 3 Mean (s.e.m.) serum levels of bilirubin (—□—) and liver enzymes (—○—, alanine aminotransferase; ---△---, asparagine aminotransferase; —■—, alkaline phosphatase) in the additional group of four rats after common bile duct (CBD) ligation and biliary decompression (BD)

patency of the anastomosis between the CBD remnant and the duodenum.

Histopathological study

CBD ligation resulted in profound changes in the liver with an increased number of bile ducts with swollen ductal cells and inflammation in the portal triads, scattered necrotic foci and inflammation also in the lobuli. After decompression, all the liver specimens showed similar findings with subsiding inflammation. The bile ducts were still prominent following biliary decompression, though less than in the CBD ligation group. There appeared to be a tendency towards a gradually decreasing inflammatory response with time following relief of biliary obstruction, as seen in group 7.

Discussion

The RES, defined as tissue macrophages located primarily in the liver, spleen, lungs and bone marrow, has been found to be responsible for the clearance of particulate matter, such as bacteria, endotoxin, immune complexes and cell debris^{12,13}. The Kupffer cells in the liver are responsible for 80–90 per cent of RES activity¹⁴. RES function is depressed in conditions such as obstructive jaundice^{15–17}, trauma¹⁸, surgery¹⁹ and sepsis²⁰. Patients with obstructive jaundice are more susceptible to sepsis, and renal insufficiency may be due to systemic endotoxaemia. This is thought to occur as a result of increased endotoxin absorption from the gut and impaired RES clearance function^{21–24}.

The increased absorption of endotoxin in obstructive jaundice has been suggested to be associated with the absence of bile salts from the small intestine. Luminal flow of bile salts has antibacterial effects²⁵ and a direct detergent effect on the endotoxin²⁶. Experimental and clinical studies with oral administration of bile salts to jaundiced animals and patients have shown a reduction of endotoxin absorption and protection from postoperative renal failure^{22,27–29}, but others^{30,31} found no endotoxaemia in animals with a choledochovesical fistula and no clinical benefit as demonstrated in jaundiced patients who received preoperative oral bile salt therapy, despite a reduction in portal endotoxin levels.

In 1935, Whipple *et al.*³² recognized the importance of biliary drainage to minimize postoperative morbidity and mortality rates in jaundiced patients. Later, percutaneous transhepatic drainage has been used as a first step before major surgery in an attempt to lower postoperative mortality rates and the incidence of infection^{33–35}. Experimental animal models of biliary decompression using internal drainage were

established for the study of liver function, biochemical, histological and immunological changes^{6–8}. Koyama *et al.*⁶ used cholecystogastrostomy in the dog, while Vane *et al.*⁷ used cholecystojejunostomy in the rabbit. Ryan *et al.*⁸, however, created a biliary decompression model in the rat with choledochoduodenostomy achieved by inserting a Teflon (Du Pont, Stevenage, UK) tube between the distended bile duct and the duodenum.

The present study developed a model for biliary decompression in the rat by performance of a choledochoduodenostomy, with anastomosis of the dilated CBD to the duodenum. We believe this model to be closer to a clinical biliodigestive anastomosis than previous ones. Although obstructive jaundice has been reported to result in suppression of specific and non-specific cellular immunity in animals^{36,37}, as well as suppression of RES function in patients and animals^{23,38–40}, the influence on immunological function of a simultaneously occurring obstructing carcinoma cannot be ruled out⁴¹. The present model has biliary obstruction as the only factor influencing RES and immunological function.

Mechanisms to remove particulate matter from the circulation by the hepatic reticuloendothelial tissue are likely to include two steps: uptake and excretion. The functional status of uptake and excretion could be evaluated by the α value in combination with the hepatic uptake of the challenged radiolabelled *E. coli* in the present study. Significantly lower α values ($P < 0.001$) and higher hepatic uptake ($P < 0.05$) in the CBD ligation group and groups 3–5 compared with controls indicate a low clearance capacity and retained degradation and excretion in those animals. However, α values in rats 3 and 5 weeks following biliary decompression (groups 6 and 7) tended to return to normal levels with no difference ($P > 0.05$) compared with controls, but hepatic uptake in these groups was still higher ($P < 0.001$) than in controls. The disappearance of intravenous *E. coli* is compatible with first-order kinetics and is completed in a very short period of time^{11,42}. The radiolabelled *E. coli* could be cleared by the rats in groups 6 and 7, 3 and 5 weeks following biliary decompression, as quickly as in controls, but were still retained in the liver owing to diminished excretion.

The full aetiology of RES depression following obstructive jaundice is unknown. Depletion of serum opsonins⁴³ and altered serum biochemistry, especially of bilirubin⁴⁴, have been considered to be leading factors. Collier *et al.*⁴⁵ found that Kupffer cells in jaundiced rats were in an 'inactivated' state. Even when toxic substances, such as bilirubin and bile salts, were removed following the relief of obstructive jaundice, improvement in mitochondrial function could not be rapidly achieved⁶. According to our experimental results of liver function tests and liver histopathology and the results reported by Ryan *et al.*⁸, histological changes in the liver are still present to a certain degree when results of liver function tests have returned to normal. Recovery of liver function test results thus precedes recovery of histological changes and RES function.

Splenic uptake has been reported to increase in compensation when hepatic RES function is depressed in obstructive jaundice⁴⁶, in agreement with the results of this study. In this series, increased pulmonary uptake of radiolabelled *E. coli* in group 4 (equivalent to 3 weeks of biliary obstruction) was found, which confirms the findings of Scott-Conner *et al.*⁴⁷ and Hansson *et al.*⁴⁸. The renal uptake of radiolabelled *E. coli* in rats with CBD ligation and groups 3 and 4 was significantly higher ($P < 0.05$) than in controls, and decreased, though not significantly, following relief of jaundice. Results in this study revealed a persisting impairment of RES function following 1–2 weeks of biliary decompression of jaundiced rats, though RES function, as estimated by the half-life of intravenously injected radiolabelled aggregated albumin, has been reported to recover rapidly (3 days) following surgical relief of obstructive jaundice⁴⁹. This impairment might be caused by both the long-term obstructive jaundice and the subsequent surgical trauma.

The present study may thus help to explain the higher incidence of sepsis and renal impairment in the early postoperative period after biliary surgery in jaundiced subjects.

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Treatment of common bile duct stones using mono-octanoin

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Endoscopic sphincterotomy and stone extraction has revolutionized the management of patients with retained and recurrent common bile duct stones¹. Nevertheless, there remains a small but important group of patients in whom the duct cannot be cleared at the time of the initial procedure. These patients are often elderly and frail and have concurrent medical problems that make them poor candidates for surgical intervention. The best way to manage such patients is not clear. Cairns *et al.*² reported 127 patients in whom endoscopic duct clearance failed and who subsequently underwent biliary drainage by nasobiliary tube or biliary stent. Duct clearance was achieved endoscopically in 41 per cent of cases and surgically in a further 20 per cent with an overall 30-day mortality rate of only 3.1 per cent.

Mono-octanoin is a cholesterol solvent that has been shown to dissolve cholesterol-containing gallstones both *in vitro* and *in vivo*³. The success rates for stone dissolution have been somewhat disappointing in clinical trials with the largest study⁴ quoting a clearance rate of only 26 per cent.

This paper presents a retrospective study which examines the role of mono-octanoin infusion in the management of patients with stones too large to be removed at initial endoscopic sphincterotomy. The results relate to the experience of a single teaching hospital with extensive referrals from within the northern region.

Patients and methods

The reports for all patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) at this hospital over the past 10 years were studied. A total of 200 patients who underwent attempted extraction of bile duct stones were identified. A satisfactory endoscopic sphincterotomy (at least 6–10 mm in size) was made in every case, with vigorous attempts at extraction of the stones using a balloon catheter. Successful duct clearance was obtained in 152 patients using the balloon catheter; stone extraction failed in 48 patients. A nasobiliary tube was inserted in 45 patients and three patients already had a T tube in the common bile duct after recent biliary surgery. The nasobiliary drain or the T tube was allowed to drain freely for 24 h before infusion of mono-octanoin at a rate of 2–4 ml h⁻¹.

Mono-octanoin infusion was attempted in all 48 patients; 31 (65 per cent) were female. The mean age was 75 (range 54–97) years. Sixteen patients (33 per cent) had undergone previous cholecystectomy, eight had also had an exploration of the common bile duct. The interval after surgery varied from 12 days to 34 years. Results of liver function tests were abnormal in all but five patients although only 32 (67 per cent) were clinically jaundiced at the time of initial ERCP.

Data relating to the size and number of stones identified were available for 40 patients. A tube cholangiogram was obtained at the end of the infusion period and if the duct was clear no further investigations were carried out. If stones remained, provided that the

A retrospective analysis of 48 patients undergoing mono-octanoin infusion via nasobiliary catheter following failure of endoscopic extraction of common bile duct stones is reported. Among 35 patients who received a complete course of treatment, nine (26 per cent) had duct clearance by the completion of the infusion and a further eight on subsequent endoscopic retrograde cholangiopancreatography (ERCP) (total 49 per cent). Two patients had a successful stone extraction after enlargement of the sphincterotomy (total non-surgical clearance rate 54 per cent). None of five patients with stones >2 cm in diameter had stone clearance at the completion of the infusion and only one at subsequent ERCP. Among 13 patients receiving an incomplete course of treatment seven had clear ducts on repeat ERCP (54 per cent). Mono-octanoin infusion via a nasobiliary catheter is of limited value in the management of this difficult group of patients, although it may be successful in some.

patient was well and the biochemical parameters had improved, the tube was removed and the patient was asked to return for repeat ERCP in 4–6 weeks.

Results

The hospital notes of 48 patients were obtained. Mono-octanoin therapy was completed in 35 patients (group 1); four patients pulled the nasobiliary tube out before infusion of mono-octanoin could be started and seven were found to have a dislodged tube on tubography performed 4–7 days after the start of infusion. In addition, two patients underwent an infusion for <4 days. These 13 patients are considered to have had incomplete treatment (group 2).

The 35 patients in group 1 received a continuous infusion of mono-octanoin for a mean of 8 (range 4–14) days. Minor side-effects were reported in 12 (27 per cent) of 44 patients who received mono-octanoin. Three patients developed abdominal pain, pyrexia and rigors whereupon the infusion was stopped. Of these three patients, two underwent emergency surgery: one recovered and the other, who was found to have a retroduodenal perforation, died. The third patient was treated conservatively because of concurrent left ventricular failure and also died. The incidence of serious complications was 7 per cent.

A tube cholangiogram was obtained in all patients except those who developed cholangitis between 5 and 10 days after the start of mono-octanoin infusion. Ten patients underwent a second tube cholangiogram, 1–21 days later. Of those who did not have a clear duct after completion of the infusion 16 of 26 subsequently underwent ERCP. This was not performed in the others because of surgical intervention (four patients), death (two), and no further symptoms (four). The results of these investigations are summarized in Table 1.

There were four deaths. One patient, who had not received an infusion, died after 2 weeks from a cerebrovascular accident. One patient died from a myocardial infarction 2 days after completing a successful infusion. One patient died from cholangitis while receiving an infusion and the other died after laparotomy for a retroduodenal perforation of the sphincterotomy. The overall 30-day mortality rate in these patients with failed stone extraction was 8 per cent.

Outcome

In group 1, clearance of the bile duct was obtained at the completion of infusion in nine patients (26 per cent). A further eight patients (23 per cent) had clear ducts on subsequent ERCP performed 4–12 weeks later. Two patients had a successful stone extraction after enlargement of the endoscopic sphincterotomy. Surgical intervention was necessary to remove

Table 1 Results of investigation in group 1 patients

Finding	First tube cholangiogram	Second tube cholangiogram	Initial ERCP	Repeat ERCP
Clear	6	3	8	2
Smaller	3	2	3	—
Unchanged	26	5	5	—
Total	35	10	16	2

ERCP, endoscopic retrograde cholangiopancreatography

residual stones in four patients, all of whom survived and were well at follow-up 6–12 weeks later.

At follow-up a total of 29 patients (83 per cent) were asymptomatic and in 23 (66 per cent) this had been achieved without surgical intervention. The non-surgical clearance rate was therefore 54 per cent (19 of 35 patients) and the overall clearance rate 66 per cent (23 of 35).

Data relating to stone size were available for 28 patients in group 1. Five patients had stones >2 cm in diameter. None of these had stone clearance at the end of the infusion as opposed to eight of the 23 with smaller stones. The overall non-surgical clearance rate in those patients with stones >2 cm in diameter was 20 per cent (one of five patients) as opposed to 61 per cent (14 of 23) for those with smaller stones.

In group 2 two patients underwent emergency surgery. This was successful in one patient; the other died. Two underwent elective surgical clearance of the bile duct with a satisfactory outcome. Of the remaining nine patients, seven had clear ducts on subsequent ERCP and two did not, but remained well without further treatment over the next year. The non-surgical clearance rate was therefore 54 per cent (seven of 13 patients) and total (surgical and non-surgical) clearance rate 77 per cent (ten of 13).

Discussion

The number of patients who have large common bile duct stones unsuitable for endoscopic extraction is small, having been reported as 8 per cent in one large series⁵. They form a group of patients who are often elderly and ill; the results of any treatment must be seen in this context.

With one exception⁴ most studies have described only small numbers of patients. In addition, they often refer to T tube infusions given for retained common bile duct stones shortly after biliary surgery^{6–10}. This series appears to be the largest single-centre study reported using nasobiliary infusion.

Initial experience with basket extraction in these circumstances had proved disappointing and resulted in basket impaction requiring operative treatment in several patients. Other methods of treatment for patients with stones that cannot be removed after endoscopic sphincterotomy have been developed during the present study period. These include mechanical lithotripsy¹¹, extracorporeal shockwave lithotripsy¹², electrohydraulic lithotripsy and various laser lithotripsy techniques^{13,14}. Many of these require complex and expensive equipment which is not widely available and experience with some of these methods is limited^{13,14}. It is therefore difficult to compare the results of this series with those using these techniques. Nevertheless, it would appear that for patients with particularly large stones in whom dissolution is not likely to be helpful these methods of treatment are going to be a significant advance.

It is not possible to isolate the effect of the mono-octanoin infusion from the overall treatment strategy used, although it must be admitted that duct clearance was no better after mono-octanoin (group 1) than in those who failed to complete the course of therapy (group 2). The fact that 54 per cent of group 2 patients were subsequently shown to have clear ducts suggests that sphincterotomy alone may be all that is necessary in some of these patients, despite the fact that the stones were not extracted at the time of sphincterotomy. Unfortunately no data are available relating to the clearance rate of stones that

cannot be extracted in the absence of further intervention, although one study¹⁵ examined the role of duct infusion via nasobiliary tube after endoscopic sphincterotomy. This resulted in duct clearance in 18 of 55 patients (33 per cent). The stone sizes in this series were, however, relatively small and a clearance rate of only 12 per cent was obtained for stones >1 cm in size. The fact that a significant proportion of the stone clearance in our series occurred after completion of the mono-octanoin infusion suggests the importance of follow-up in the study of efficacy of treatment.

If the aim of treatment is considered to be an asymptomatic patient rather than a clear common bile duct, then this was achieved in 83 per cent of patients in this series. We conclude that most patients with large common bile duct stones that are unsuitable for endoscopic extraction can be managed without recourse to surgery with a reasonable prospect of success. The management of these patients must be considered carefully on an individual basis and no single method appears satisfactory in all cases. It is doubtful whether mono-octanoin adds anything to the management of these patients. The aims of treatment should be to drain the biliary system adequately by endoscopic sphincterotomy with or without a drainage catheter and, if possible, to clear the duct of stones. Many stones which cannot be extracted at the time of the initial endoscopic sphincterotomy will subsequently pass or can be removed at a second procedure.

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Risk factors and classification of acute suppurative cholangitis

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A prospective study was performed in 1282 patients with common bile duct stones to determine the clinical and laboratory parameters that could predict cholangitis, and the factors associated with greater severity of cholangitis. Patients were divided into two groups, with or without acute cholangitis, depending on the macroscopic appearance of bile aspirated from the common bile duct during surgery. Acute cholangitis was diagnosed when the aspirated fluid was turbid or clearly pus; the typical Charcot's triad was present in only 22 per cent of patients with acute cholangitis. Several clinical and laboratory parameters were significantly more common in these patients and, depending on their number, the probability of acute cholangitis increased significantly. The operative mortality rate was 1.2 per cent for patients without cholangitis and 11.9 per cent for patients with cholangitis. Depending on the number of factors present, patients with cholangitis were divided into three groups: mild acute cholangitis without mortality; moderate acute cholangitis with a mortality rate of 5.6 per cent; and severe acute cholangitis with a mortality rate of 27.5 per cent. The present classification allows the group of patients needing prompt endoscopic or surgical drainage to be identified.

Acute suppurative cholangitis is a serious complication in patients with extrahepatic obstruction of the biliary tract secondary to many causes¹⁻¹⁰, but in our experience it is due to the presence of common bile duct (CBD) stones in 80 per cent of cases¹¹. The reported mortality rate has ranged from 10 to 80 per cent¹⁻¹⁰, probably owing to different diagnostic and therapeutic approaches.

The purpose of the present prospective study was to analyse a homogeneous group of patients, comprising only those with CBD stones. Patients were grouped according to whether or not they had acute cholangitis. Clinical and laboratory parameters that could predict the presence of cholangitis were determined, along with factors associated with a greater risk of death. A classification of the severity of acute cholangitis was established.

Patients and methods

Patients

The present study is a prospective analysis of the surgical management of all patients with CBD stones seen at this department between 1980 and 1988. There were 1282 patients from a total of 15 200 with benign biliary tract disease operated on during this period. There were 960 women and 322 men of mean age 45.4 (range 17-84) years. Only patients with extrahepatic CBD stones were included; patients with concurrent intrahepatic stones, benign strictures, carcinoma of the gallbladder or biliary tract or cholecystoenteric fistula were excluded.

Patients were divided into two groups according to the macroscopic appearance of bile aspirated from the CBD during surgery:

1. Patients without acute suppurative cholangitis; the aspirated fluid from the CBD was clear green bile.
2. Patients with acute suppurative cholangitis; the aspirated fluid was turbid or frank pus.

The protocol documented 51 different clinical, laboratory and surgical findings. Three main aspects were studied in both groups: clinical and laboratory parameters that could predict the presence of cholangitis before any therapeutic approach; risk factors of operative mortality; and classification of acute suppurative cholangitis according to its severity.

Determination of the presence of common bile duct stones

In each case, one or more stones in the extrahepatic duct were identified

during surgical exploration of the CBD. Ultrasonography was performed before surgery in every case and was positive for stones in the CBD in 65 per cent. In some patients, percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography was performed before surgery for diagnostic purposes.

Histology

All resected gallbladders were submitted to histological study to exclude carcinoma. In several patients liver and bile duct biopsies were also taken for another study¹².

Operation

After laparotomy and abdominal exploration, the extrahepatic biliary tract was assessed. The macroscopic appearance of the gallbladder, presence of gallstones and diameter of the cystic duct were noted. The external diameter and intraluminal pressure of the CBD were measured^{12,13}. Before opening the CBD, a bile sample was aspirated to assess its macroscopic appearance and for bacteriological analysis¹¹. The number of stones in the CBD and the presence of any impacted stones were determined. An impacted stone was defined as one which had the same size as the internal diameter of the CBD and which could not easily be displaced by manoeuvres to extract it; often crushing was required to allow extraction.

In all cases choledochostomy using a 14- or 16-Fr T tube was performed. When the gallbladder was present (in 90 per cent of cases), cholecystectomy was performed. A latex drain was left in the subhepatic space for 2 days. Antibiotics were administered in patients with acute cholangitis. A T tube cholangiogram was performed in all patients 12-15 days after surgery.

Statistical analysis

For statistical evaluation the χ^2 test and analysis of variance were employed. A *P* value < 0.05 was considered to be significant.

Results

Of 1282 patients with CBD stones, 770 (60 per cent) had clear green bile in the biliary tract and 512 (40 per cent) turbid or purulent bile. The latter were defined as patients with acute suppurative cholangitis. The sex distribution was similar in both groups, but the mean age of patients with cholangitis was 50 years, significantly older than the mean age of 40 years for patients without cholangitis (*P* < 0.001). The main clinical

Table 1 Clinical findings in 1282 patients with common bile duct stones

Clinical findings	Without cholangitis (n = 770)	With cholangitis (n = 512)	P*
Age > 60 years	200 (26.0)	209 (40.8)	<0.001
Biliary colic	667 (86.6)	472 (92.2)	>0.2
Jaundice	359 (46.6)	335 (65.4)	<0.01
Fever or chills	161 (20.9)	198 (38.7)	<0.001
Concomitant disease	90 (11.7)	199 (38.9)	<0.04
Rectal temperature > 38°C	116 (15.1)	157 (30.7)	<0.001
Mental confusion	8 (1.0)	37 (7.2)	<0.001
Shock	8 (1.0)	36 (7.0)	<0.001

Values in parentheses are percentages. * χ^2 test**Table 2** Laboratory findings in 1282 patients with common bile duct stones

Laboratory findings	Without cholangitis (n = 770)	With cholangitis (n = 512)	P*
Bilirubin > 34 mmol/l	359 (46.6)	335 (65.4)	<0.001
Aspartate transaminase > 21 units/l	476 (61.8)	367 (71.7)	<0.0003
Blood glucose > 9.9 mmol/l	60 (7.8)	93 (18.2)	<0.001
Blood urea nitrogen > 7.5 mmol/l	72 (9.4)	112 (21.9)	<0.001
Leucocytes > 12000/mm ³	129 (16.8)	160 (31.2)	<0.001
Left deviation > 16 per cent	119 (15.5)	186 (36.3)	<0.001
Lymphocytes < 1000/mm ³	236 (30.6)	205 (40.0)	<0.0007
Prothrombin time > 15 s	227 (29.5)	224 (43.8)	<0.001
Alkaline phosphatase > 200 units/l	184 (23.9)	149 (29.1)	>0.3
Haemoglobin < 14 g/dl	368 (47.8)	274 (53.5)	>0.4

Values in parentheses are percentages. * χ^2 test**Table 3** Preoperative versus final diagnosis in 1282 patients with common bile duct stones

Preoperative diagnosis by surgeon	Final diagnosis	
	No cholangitis (n = 770)	Cholangitis (n = 512)
No cholangitis	672 (87.3)	113 (22.1)
Cholangitis	98 (12.7)	399 (77.9)

Values in parentheses are percentages

findings are shown in Table 1. The presence of classical Charcot's triad (pain, fever or chills, and jaundice) and Reynolds' pentad (including mental confusion and shock) at admission were determined. Although Charcot's triad was present in 22 per cent of patients with acute cholangitis, it was present in only 9 per cent of those without cholangitis. The incidence of Reynolds' pentad was very low.

The main laboratory findings of both groups are shown in Table 2. There were eight parameters that were significantly more frequent in patients with cholangitis. The comparison of preoperative diagnosis of acute cholangitis by the treating surgeon and the intraoperative finding of pus in the CBD is shown in Table 3. The correct preoperative diagnosis of absence of cholangitis was made in 87 per cent of cases and the correct preoperative diagnosis of cholangitis was made in 78 per cent of cases. It was possible to determine, by computer analysis, 16 parameters that were individually more frequent in patients with acute cholangitis compared with patients without cholangitis. These parameters were: age over 60 years; presence of concomitant disease; shorter duration of biliary colic; jaundice before admission; fever or chills before admission; jaundice, shock, mental confusion and rectal temperature

> 38°C at admission; aspartate transaminase level > 21 units/l; leucocytes > 12000/mm³; left deviation > 16 per cent; lymphocytes < 1000/mm³; prothrombin time > 15 s; blood urea nitrogen > 7.5 mmol/l; and blood glucose > 9.9 mmol/l. Using these findings, it was possible to establish the probability of the presence of acute cholangitis according to the increasing number of parameters present, as shown in Table 4. It can be seen that, with six factors present, the probability of acute cholangitis is about 50 per cent; with eight factors, the probability of acute cholangitis is over 80 per cent.

There were no differences in gallbladder features between groups (Table 5). However, the diameter of the CBD and the incidence of impacted stones were significantly greater in patients with acute cholangitis ($P < 0.003$).

Patients with acute cholangitis had significantly more complications after operation than those without cholangitis (Table 6). The mortality rate for patients with acute cholangitis was ten times greater than for patients without cholangitis. The incidence of residual CBD stones was similar. The use of routine intraoperative cholangiography started at the end of the present study. By statistical analysis, it was possible to determine five factors significantly associated with operative mortality in patients without cholangitis (Table 7). The number of risk factors present and associated mortality rate in patients without cholangitis are shown in Table 8. There is an increasing mortality rate with an increasing number of risk factors present in each patient. However, it should be noted that in 97.5 per cent of patients there were two or fewer risk factors present and the mortality rate was 0.7 per cent. Only the 19 remaining cases (2.5 per cent) had a mortality rate of 21 per cent, bringing the mean mortality rate for the whole group to 1.2 per cent.

Table 4 Presence before surgery of clinical and laboratory factors associated with cholangitis related to final diagnosis in 1282 patients

No. of factors present	No. of patients (n = 1282)	No. of patients with acute cholangitis (n = 512)
0	20	2 (10)
1	153	18 (11.8)
2	186	45 (24.2)
3	211	67 (31.8)
4	229	91 (39.7)
5	172	75 (43.6)
6	113	62 (54.9)
7	100	68 (68.0)
8	50	41 (82)
9	32	28 (88)
10	9	8 (89)
11	3	3 (100)
12	4	4 (100)

Values in parentheses are percentages

Table 5 Operative findings in 1282 patients with common bile duct stones

Findings	Without cholangitis (n = 770)	With cholangitis (n = 512)	P*
Gallbladder present	696 (90.4)	455 (88.9)	>0.4
Two or more stones in gallbladder	641 (83.2)	431 (84.2)	>0.2
Cystic duct diameter > 6 mm	439 (57.0)	312 (60.9)	>0.2
Common bile duct diameter > 10 mm	487 (63.2)	398 (77.7)	<0.003
Common bile duct stones			
1 or 2	458 (59.5)	310 (60.5)	>0.2
3-5	139 (18.1)	95 (18.6)	
6-9	40 (5.2)	28 (5.5)	
≥ 10	133 (17.3)	79 (15.4)	<0.003
Impacted stone	142 (18.4)	161 (31.4)	

Values in parentheses are percentages. * χ^2 test

Table 6 Morbidity and mortality after operation in 1282 patients with common bile duct stones

Postoperative state	Without cholangitis (n = 770)	With cholangitis (n = 512)	P*
Well	753 (97.8)	390 (76.2)	<0.001
Morbidity	36 (4.7)	61 (11.9)	<0.001
Haemoperitoneum	5 (0.6)	4 (0.8)	<0.001
Bile peritonitis	9 (1.2)	19 (3.7)	<0.001
External biliary fistula	5 (0.6)	6 (1.2)	<0.001
Pulmonary infection	12 (1.6)	24 (4.7)	<0.001
Subphrenic abscess	5 (0.6)	8 (1.6)	<0.001
Residual common bile duct stones (excluding deaths)	62 (8.1)	51 (10.0)	>0.2
Mortality	9 (1.2)	61 (11.9)	<0.001

Values in parentheses are percentages. * χ^2 test

Table 7 Factors associated with operative mortality in 1282 patients

Without cholangitis (n = 770)	With cholangitis (n = 512)
Age > 60 years	Age > 60 years
Concomitant disease	Concomitant disease
Haemoglobin < 11 g/dl	Duration of colic > 8 days
Blood urea nitrogen > 10.7 mmol/l	Jaundice previous to and at admission
Diameter of common bile duct > 20 mm	Mental confusion
	Shock at admission
	Blood urea nitrogen > 10.7 mmol/l
	Blood glucose > 9.9 mmol/l
	Haemoglobin < 11 g/dl
	Left deviation > 16 per cent
	Prothrombin time > 20 s
	Alkaline phosphatase > 200 units/l
	Diameter of common bile duct > 20 mm

Table 8 Risk factors associated with operative mortality in 770 patients without acute cholangitis

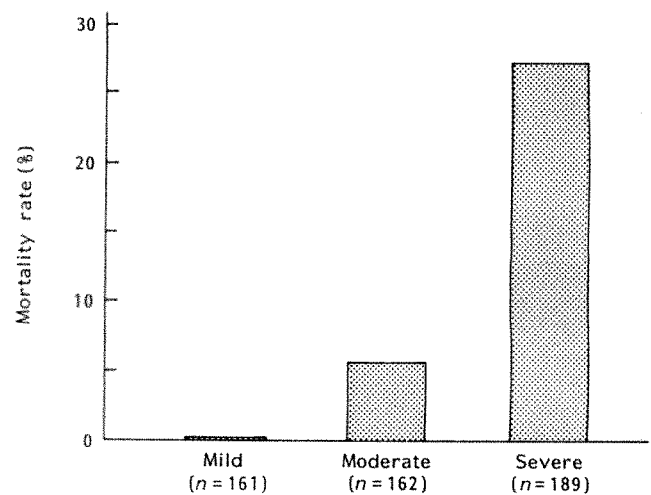
No. of factors	No. of patients	No. of deaths
0	390	0 (0)
1	255	2 (0.8)
2	106	3 (2.8)
3	16	3 (19)
4	3	1 (33)
Total	770	9 (1.2)

Values in parentheses are percentages

Table 9 Risk factors associated with operative mortality in 512 patients with acute suppurative cholangitis

No. of factors	No. of patients	No. of deaths	Severity of disease
0	15	0 (0)	Mild
1	61	0 (0)	
2	85	0 (0)	
3	84	4 (5)	Moderate
4	78	5 (6)	
5	77	15 (19)	Severe
6	61	15 (25)	
7	23	9 (39)	
8	22	10 (45)	
9	6	3 (50)	

Values in parentheses are percentages

**Figure 1** Operative mortality rate in acute suppurative cholangitis according to severity of disease

The risk factors in patients with acute cholangitis are shown in Table 9. There was an increasing mortality rate up to 50 per cent according to the number of risk factors present. However, three groups of patients may be defined as shown in Figure 1: (1) patients with mild disease, with up to two factors present, without mortality; (2) patients with moderate disease, with three or four factors present, with a mortality rate of 5.6 per cent; and (3) patients with severe disease, with five to nine factors present, with a mortality rate of 27.5 per cent. Each group corresponded to about one-third of the cases. The main cause of death was sepsis.

Discussion

Definition of acute suppurative cholangitis

There is no consensus regarding the definition of acute suppurative cholangitis. Should it be defined clinically by the presence of Charcot's triad, or by the surgical finding of pus in the CBD, or by its systemic effects? The typical Charcot's triad was present in only 22 per cent of patients with pus and 9 per cent of patients with clear green bile. Charcot's triad has been found in 50–70 per cent of patients in other studies^{6,8}. Clinical definition seems to be very imprecise, possibly because of varying severity of disease in different studies^{1–10,13}. Acute suppurative cholangitis has a wide spectrum of severity; the simple presence of pain, fever or chills, and jaundice may not be very helpful diagnostically, and there are other conditions with similar clinical patterns. An attempt was made to define acute suppurative cholangitis by the presence of bacteria in the CBD. In a previous study¹¹, it had been found that 75 per cent of patients with CBD stones and clear bile had cultures positive for bacteria, rising to 90 per cent in patients with pus in the CBD. The number of organisms, the bacterial species and the sensitivity to antibiotics were similar in both groups. It seems that the presence and characteristics of the bacteria in the CBD are not helpful in distinguishing acute suppurative cholangitis. Therefore we believe that the easiest and most practical way to define the presence of this condition is by the presence of turbid bile or pus in the CBD, aspirated percutaneously through the liver, by endoscopic cannulation, or during surgery.

We propose to abandon the term 'acute non-suppurative cholangitis'⁶, which describes patients with partial obstruction of the CBD who have green bile. Bacteria are frequently cultured from these patients and the terminology of 'non-suppurative cholangitis' can lead to misunderstanding. We propose to employ a simple definition of only two states: patients with and patients without acute cholangitis, based on whether they do or do not have turbid bile or pus in the CBD.

Clinical diagnosis of acute suppurative cholangitis

The clinical diagnosis of acute suppurative cholangitis can be erroneous, failing to recognize a proportion of patients with pus in the CBD. However, experienced surgeons can establish a proper diagnosis based on several clinical and laboratory patterns in nearly 80 per cent of cases, and can exclude the presence of pus in the CBD in nearly 88 per cent of patients before surgical exploration. However, this relates only to patients with CBD stones, not to those with intrahepatic stones, strictures of the CBD or carcinoma. In the present study, several easily obtained clinical and laboratory parameters have been noted that can predict the presence of acute suppurative cholangitis. These parameters are reproducible and, therefore, very useful. If properly used, a prompt endoscopic^{14,15} or surgical decompression of the CBD may be employed with a minimum of error.

Definition of severity of acute suppurative cholangitis

We feel that it is necessary to define acute suppurative cholangitis more objectively. Using some clinical parameters, severe forms of cholangitis have been referred to as suppurative on the presumption that pus is present in the obstructed biliary tree^{6,10,16}. This implies that there is a non-suppurative form of cholangitis (bacteria present without pus) which is less severe and has a better outcome. However, O'Connor *et al.*¹⁷ and Boey and Way⁶ reviewed patients with cholangitis and could not find a strong correlation between clinical manifestations and pus in the CBD at laparotomy. The belief that the presence of pus identifies all patients with the severest form of disease has led to error and confusion. Pus in the CBD does not correlate well with the severity of the clinical picture of this disease, which exhibits a very wide spectrum of presentation¹. Because of this we have tried to identify risk factors to define severity of disease. If no pus is present, the mortality rate for 97.5 per cent of cases is only 0.7 per cent; there is a small group of patients (2.5 per cent) with clear green bile who have a high mortality rate. In contrast, patients with pus in the CBD can be divided into three groups, according to disease severity, which are each approximately one-third of the total. Mild disease carries a zero mortality rate, moderate disease 6 per cent, and severe disease 28 per cent. This finding explains why some patients with pus have a good outcome from acute suppurative cholangitis. On the other hand, the severe group is probably that which several authors have studied; these patients require prompt surgical or endoscopic drainage.

The present classification of the severity of acute cholangitis may have practical importance; it neatly describes the wide spectrum of this disease, it can help to decide in whom drainage of the biliary tract should be performed urgently, and it permits a proper comparison of the results of different series from different authors. However, the classification has been applied only to patients with CBD stones¹⁸. We cannot accept the propriety of analysing risk factors when several disparate groups are evaluated together, as others have done¹⁹⁻²¹. It is improper to group patients with stones together with those having carcinoma of the bile duct or pancreas, or to group simple choledochostomy with hepaticojejunostomy or with a Whipple's procedure. For these reasons we have studied a

homogeneous group to establish an objective classification; it will be necessary for others to evaluate our findings to determine their reproducibility.

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Identification of the regional lymphatic system of the gallbladder by vital staining

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In 21 patients with biliary tract cancer dye was injected into the lymphatic system of the gallbladder to determine the extent of its regional lymph nodes. A volume of 0.1-0.3 ml 1 per cent indigo carmine solution was injected directly into lymphatic vessels of the gallbladder in eight patients and into lymph nodes (cystic node or pericholedochal nodes) in 13 patients during radical surgery for biliary tract cancer. The lymphatic system was visualized in a total of 14 patients. The dye descended around the bile duct, flowed into the cystic node, the pericholedochal nodes and the lymph nodes posterior to the head and neck of the pancreas, and finally reached the interaortocaval nodes adjacent to the left renal vein. The stained lymphatic tissue was regarded as the regional lymphatic system of the gallbladder. These nodes should be completely resected during radical surgery for gallbladder cancer.

In recent years radical surgery with extensive resection of regional lymph nodes has been advocated for the treatment of gallbladder carcinoma¹⁻⁴. Defining the extent of the regional gallbladder lymph nodes that should be removed during this radical surgery has become an important issue.

Investigators have examined the route of lymph flow from the gallbladder both anatomically and clinically⁵⁻⁸. These studies have demonstrated that the cystic node and the pericholedochal nodes are the 'first echelon' nodes of the gallbladder. However, further definition of the route of lymphatic drainage is lacking.

This study was conducted to clarify the route of gallbladder lymphatic drainage and the distribution of regional lymph nodes by dye injection^{9,10}. The aim was to define a practical goal for lymph node dissection in radical surgery for gallbladder carcinoma.

Patients and methods

From 1987 to 1990, dye injection studies were performed in 31 patients with gallbladder or bile duct cancer during radical surgery. All gave informed consent for the study. Patients with marked malignant involvement of the regional lymph nodes of the gallbladder were excluded from the study because lymph flow was altered by the involved nodes in these cases.

In the first ten patients, dye was injected into the wall of the gallbladder without regard to the location of lymphatic vessels. However, the dye did not move from the site of injection after 20-115 min and failed to demonstrate the lymphatic system of the gallbladder. Thereafter, injection of the dye directly into the lymphatic system (lymphatic vessel or lymph node) was attempted in the remaining 21 patients.

A small volume (0.1-0.3 ml) of 1 per cent indigo carmine dye solution (Wako Pure Chemical Industries, Osaka, Japan) was injected directly into a lymphatic vessel of the gallbladder or into the cystic and/or pericholedochal nodes using a disposable syringe with a 27-Fr needle by the following two methods.

Direct injection into lymphatic vessels of the gallbladder

Direct puncture of a large lymphatic vessel of the gallbladder was attempted in eight patients. Only a few large lymphatic vessels underneath the serosa of the neck or body of the gallbladder were visible unless pericholecystic adhesion or marked cholecystitis was present. The hepaticoduodenal ligament just distal to the gallbladder was compressed between the fingers to distend the lymphatic vessels. These were punctured with the needle and dye was gently injected. The

lymphatic system stained rapidly and was recorded as quickly as possible because the dye washes out after only a few minutes.

Direct injection into regional lymph nodes of the gallbladder

Dye was injected into the first echelon regional lymph nodes of the gallbladder (either the cystic node or pericholedochal nodes) in 13 patients. Before injection, a Kocher manoeuvre to mobilize the pancreaticoduodenal region was carried out to expose the posteriorly located lymphatic system. Puncture of the node was easily performed, unless a small lymph node was buried in excessive adipose tissue. The distribution of the regional lymph nodes was quickly recorded before the dye was washed out.

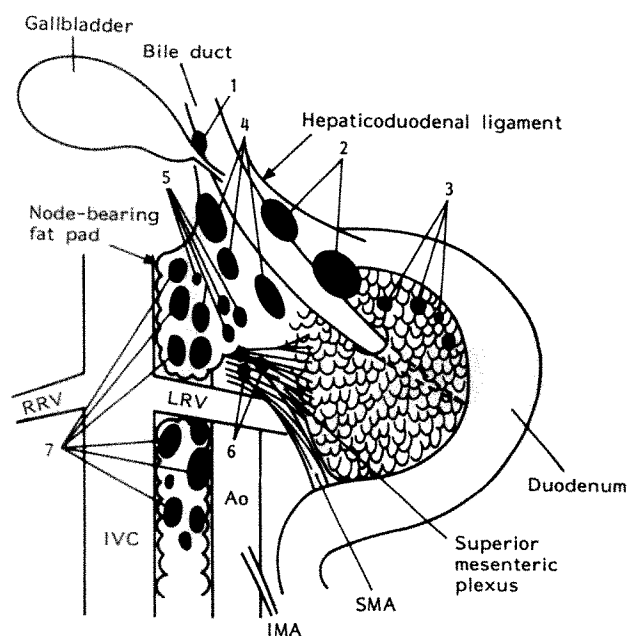


Figure 1 Schematic representation of the nomenclature and location of lymph nodes associated with the gallbladder. The head of the pancreas is raised medially to expose posteriorly located lymph nodes. Arabic numerals indicate each group of lymph nodes: 1, cystic (duct) node(s); 2, pericholedochal nodes; 3, posterosuperior pancreaticoduodenal nodes; 4, retroportal nodes; 5, right coeliac nodes; 6, superior mesenteric nodes; 7, interaortocaval nodes. Ao, aorta; IVC, inferior vena cava; SMA, superior mesenteric artery; IMA, inferior mesenteric artery; LRV, left renal vein; RRV, right renal vein

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Nomenclature

The nomenclature of lymph nodes associated with the hepatopancreaticobiliary system is not standardized^{7,11-13}. In the present study the lymph nodes were named as illustrated in Figure 1. The interaortocaval nodes exist in node-bearing adipose tissue of the retroperitoneum between the aorta and the inferior vena cava and belong to the lymphonodi lumbales (Paris nomina anatomica).

Results

Direct injection into lymphatic vessels of the gallbladder

The lymphatic system was demonstrated in four of eight patients. Figure 2 illustrates a typical example of the lymphatic system visualized by this method. It was observed that the injected dye spread immediately into the network of the subserosal lymphatics and flowed into two or three trunks located in the neck of the gallbladder. The dye then drained into the lymphatic vessels around the bile duct and into the pericholedochal nodes. Thereafter it descended towards the node-bearing adipose tissue posterior to the head of the pancreas and portal vein. The pericholedochal and retroportal nodes were observed to stain but dye never ascended towards the hepatic hilum.

Direct injection into regional lymph nodes of the gallbladder

This method was attempted in 13 patients. The dye was injected into the pericholedochal nodes in eight patients and into the cystic node in two. Lymph node puncture was unsuccessful in the remaining three patients.

Figure 3 shows the lymphatic system demonstrated by injection of dye into the pericholedochal node. In all cases dye drained into the retroportal and posterosuperior pancreaticoduodenal nodes, and then into the right coeliac nodes behind the common hepatic artery. The additional lymph nodes visualized by injection of dye are termed the 'second echelon'

nodes of the gallbladder. They are interconnected by a network of lymphatic vessels that is located on the posterior surface of the upper half of the head and neck of the pancreas, as shown in Figure 3. Interestingly, in six of eight cases dye drained directly from the retroportal, pericholedochal, posterosuperior pancreaticoduodenal and right coeliac nodes into the node-bearing adipose tissue between the aorta and the inferior vena cava adjacent to the left renal vein. This pattern demonstrates that the second echelon nodes of the gallbladder connect directly with the interaortocaval nodes. In two cases the lymphatic connection between the second echelon nodes and the interaortocaval nodes was not recognized, probably because of extensive operative mobilization in the pancreaticoduodenal region.

Dye that was injected into the cystic node descended in the lymphatics around the bile duct and then drained into the pericholedochal and retroportal nodes. Subsequently the pericholedochal, retroportal and interaortocaval nodes became stained. Upward progress of dye towards the hepatic hilum was not observed.

Summary of identified routes of lymphatic drainage of the gallbladder

The results obtained from direct injection of dye into lymphatics or lymph nodes are summarized in Figure 4. The lymph of the gallbladder descends around the bile duct, and via first echelon (cystic and pericholedochal) nodes flows into second echelon nodes posterior to the pancreas, portal vein and common hepatic artery and on to the interaortocaval nodes.

The first and second echelon nodes that were stained with dye are regarded as the regional lymph nodes of the gallbladder. The interaortocaval nodes adjacent to the left renal vein are considered the final nodes of the regional lymphatic system of the gallbladder.

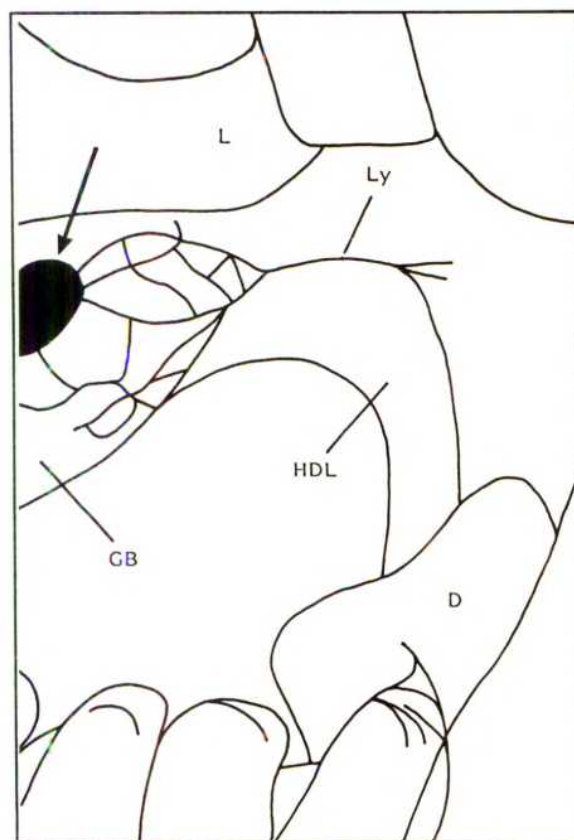


Figure 2 Direct injection of indigo carmine solution into a large lymphatic vessel in the subserosa of the gallbladder. The arrow indicates the site of injection. **a** Via the network of lymphatic vessels of the gallbladder, dye flowed downwards into lymphatic vessels around the bile duct. **b** Schematic representation of **a**. Note the network of large lymphatic vessels of the gallbladder and the descending lymphatic vessels along the bile duct. Ly, stained lymphatic vessels; GB, gallbladder; HDL, hepaticoduodenal ligament; D, duodenum; L, liver

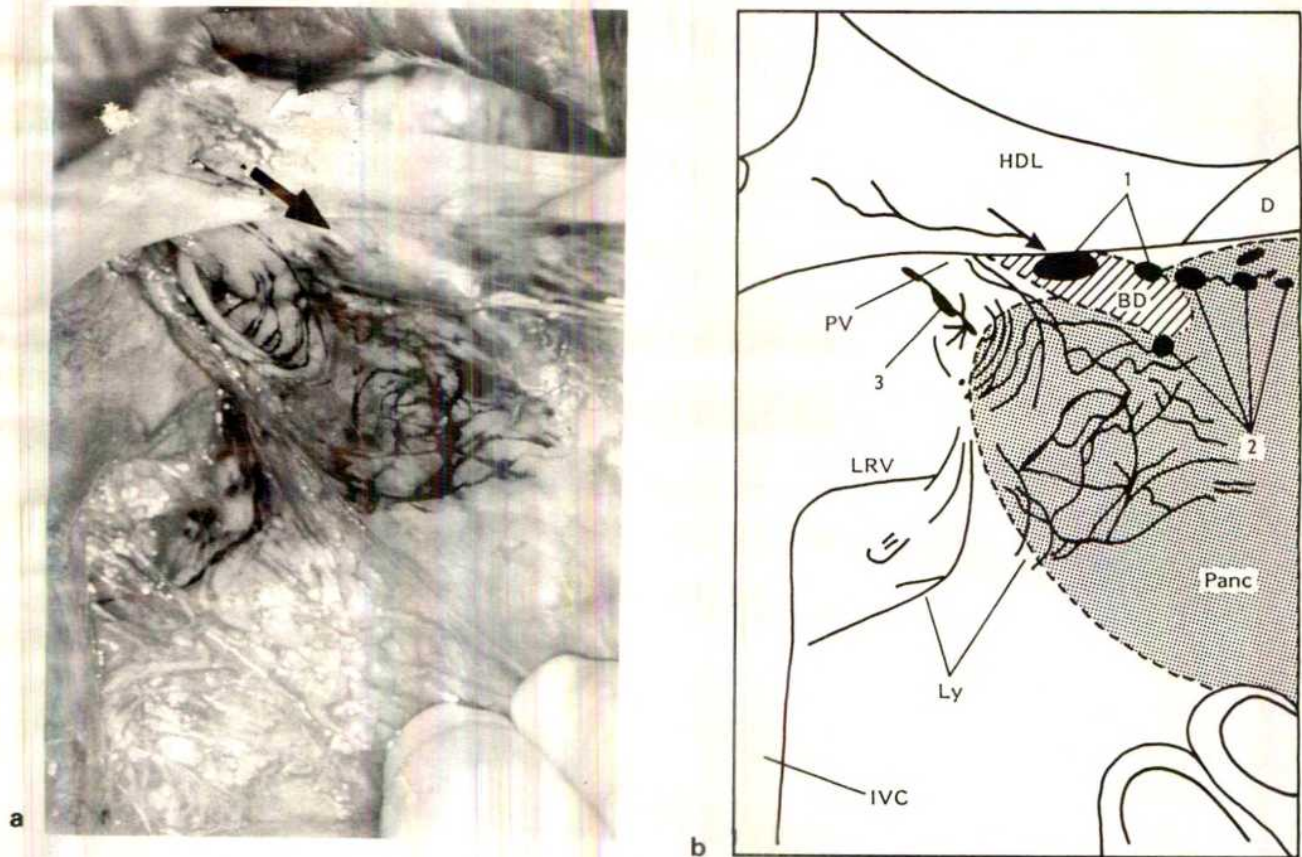


Figure 3 Direct injection of indigo carmine solution into a pericholedochal node, one of the first echelon nodes of the gallbladder. The head of the pancreas is elevated medially to expose the posteriorly located lymphatic system. The arrow indicates the site of dye injection. **a** Note that the dye flows through an intricate network of lymphatic vessels behind the head of the pancreas into second echelon nodes and finally into the interaortocaval region. **b** Schematic representation of **a**. Note the intricate network of lymphatics behind the pancreas and the lymphatic vessels that connect with the interaortocaval region. Arabic numerals indicate the stained lymph nodes: 1, pericholedochal nodes; 2, posterosuperior pancreaticoduodenal nodes; 3, retroportal nodes. Ly, stained lymphatic vessels; HDL, hepaticoduodenal ligament; D, duodenum; PV, portal vein; BD, bile duct; LRV, left renal vein; Panc, pancreas (posterior surface of the head); IVC, inferior vena cava

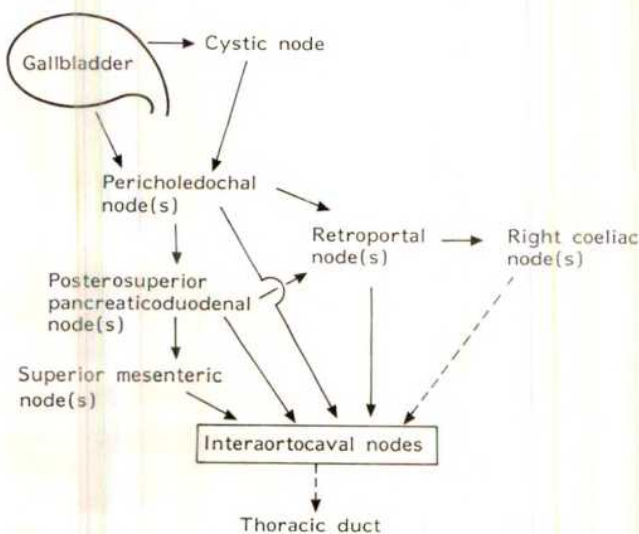


Figure 4 Diagrammatic representation of the regional lymph nodes of the gallbladder. The arrows indicate the principal routes and the directions of lymph flow from the gallbladder. The broken arrows indicate probable routes, although they were not observed in this study because of the presence of adipose tissue surrounding them

Discussion

In the 1950s Weinberg *et al.* reported that dye injection was a safe and useful method for visualization of regional lymphatics during surgery for gastric and lung cancer^{9,10}. In the present study this method was applied to surgery for gallbladder or

bile duct cancer. This has clarified the extent of the regional lymph nodes of the gallbladder.

Weinberg and Greaney reported that injection of dye into the stomach wall could demonstrate its regional lymphatic system⁹. However, in the present study it was found that injection of dye into the wall of the gallbladder was unable to visualize its regional lymphatic system. Direct injection of dye into the lymphatics or lymph node was necessary.

Some investigators have reported that the cystic and pericholedochal nodes are the first station regional nodes of the gallbladder⁵⁻⁷. The further routes of lymph flow remain unclear. Extensive and rational dissection of lymph tissue in radical surgery for gallbladder cancer requires more detailed knowledge of regional lymph node location and of the direction of lymph flow^{4,14}.

Route of lymph flow

Lymph that originates from the gallbladder descends around the bile duct, flows into the lymph nodes posterior to the pancreas and finally flows into the interaortocaval nodes near the left renal vein.

Ascending lymph flow towards the hepatic hilum was not observed. In a study in the dog Kambayashi found that lymph from the gallbladder ascended towards the hepatic hilum if lymph flow was blocked by ligation of lymphatics in the hepaticoduodenal ligament¹⁵. Unless lymphatics are blocked by metastatic cancer, inflammatory changes or operative ligation, lymph of the gallbladder descends in the ligament towards the head of the pancreas. Valvules in the large lymphatic vessels of the gallbladder or the adipose tissue adjacent to the gallbladder may prevent retrograde flow and explain why lymph flows inferiorly¹⁶.

Regional lymph nodes

The regional lymph nodes of the gallbladder are illustrated in Figure 4. These show high rates of metastasis in clinical practice^{4,14}. The regional lymph nodes include those along the bile duct, second station nodes posterior to the pancreas, and finally the interaortocaval nodes adjacent to the left renal vein. The efferent lymphatic vessels of the interaortocaval nodes connect directly with the thoracic duct^{5,17}.

The nomenclature of regional lymph nodes of the gallbladder was proposed in the tumour node metastasis (TNM) staging system^{11,12}, but the exact sites are not illustrated in this classification. The Japanese Society of Biliary Surgery has presented its own classification of the regional lymph nodes¹³, and other nomenclatures have also been suggested⁵⁻⁸. A standardized nomenclature is needed. We propose the system outlined above, and summarized in Figure 4. First station nodes are found around the gallbladder and bile duct, second station nodes behind the pancreas and around the hepatic vessels. Interaortocaval nodes represent the final nodes of the regional lymphatic drainage of the gallbladder.

Lymph node dissection

Since 1982, in this department resection of the entire regional lymphatic system has been attempted during radical surgery for advanced gallbladder cancer^{4,14}. We believe that our successful results justify a strategy of extensive lymph node dissection.

When nodal dissection during radical surgery for gallbladder cancer is performed, all stromal tissue located in the hepaticoduodenal ligament and posterosuperior to the head of the pancreas should be removed *en bloc* by skeletonization of neighbouring structures such as the portal vein and hepatic artery. Metastatic disease in the interaortocaval nodes is regarded as distant metastasis, i.e. systemic disease, in the TNM staging system^{11,12}. However, this study classifies the interaortocaval nodes as the final regional nodes of the gallbladder and considers metastasis to them as regional disease. Although resection of the node-bearing adipose tissue posterior to the pancreas is rather difficult, complete radical resection of all regional nodes including the interaortocaval nodes should improve survival rates for this disease.

Acknowledgements

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Bile duct stents in the management of hepatolithiasis with long-segment intrahepatic biliary strictures

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Biliary stricture represents a challenging problem in the treatment of hepatolithiasis because of its association with treatment failure and stone recurrence. The long-segment type of stricture is difficult to manage and is likely to recur. To investigate the necessity for biliary stenting after balloon dilatation therapy, 20 consecutive patients with long-segment strictures who had 22 stents (group 1) were compared with ten patients who refused stenting (group 2). The long-segment strictures in group 1 were located on the right side in 80 per cent of patients, on the left side in 10 per cent, and were bilateral in 10 per cent. The stents, varying from 8 to 12 Fr, were retained for at least 6 months. They were inserted through the routes of a matured T tube track (five cases), percutaneous transhepatic track (14 cases), a jejunal limb (two cases) and a fistula (one case). Complications of stenting consisted of dislodgement (one case), haemobilia (two cases), cholangitis (two cases) and intrahepatic abscess (one case). The cumulative probability of stricture recurrence in group 1 was 10 per cent, 15 per cent and 21 per cent at 2, 3 and 4 years, respectively, whereas in group 2 it was 80 per cent at 2 years ($P < 0.003$). The results suggest that intrahepatic biliary stenting after balloon dilatation appears necessary and helpful in the management of hepatolithiasis with long-segment biliary strictures.

Intrahepatic biliary stricture, with or without ductal angulation, makes hepatolithiasis difficult to treat and usually necessitates repeated interventions¹⁻⁷. The main objectives of treatment consist of complete stone removal and elimination of bile stasis, and are often limited by retention or reformation of calculi at the stricture sites^{1,2,4}. Aggressive treatment is needed to prevent the sequelae of hepatolithiasis such as suppurative cholangitis, septicaemia and secondary biliary cirrhosis with resultant hepatic failure.

In Asia, three-quarters of patients with hepatolithiasis have an associated biliary stricture. In Taiwan, where hepatolithiasis is quite prevalent, the incidence of biliary stricture is as high as 91 per cent³. In the management of retained or recurrent calculi after surgery, it is necessary to deal with the intrahepatic biliary strictures as well as the stones^{2,4}. For left hepatic duct stricture, the most frequent category, left lateral segmentectomy or left hepatectomy is the preferred treatment. It is more difficult to treat right-sided strictures. Intrahepatic balloon dilatation therapy through the track formed by the postoperative T tube, or by percutaneous transhepatic biliary drainage with the assistance of choledochoscopy, appears to be the most successful form of treatment apart from, perhaps, liver transplantation⁴.

Strictures > 1.5 cm in length are especially difficult to treat, with a high potential for resticture, reformation of calculi and recurrent cholangitis. Such patients have a high risk of fatal sepsis. The main aim of treatment must be to maintain the dilatation and to prevent resticture. This study has analysed patients with long-segment strictures to determine the long-term patency rate and the risk of complications after intrahepatic stenting following dilatation.

Patients and methods

The usual treatment for hepatolithiasis in this hospital includes operation and postoperative cholangioscopic lithotomy through the T tube track or by the percutaneous transhepatic route. From July 1983 to June 1990, a total of 480 patients with hepatolithiasis received surgical treatment. The incidence of intrahepatic biliary stricture was 85.0 per cent (408 of 480 patients). Among those 408 patients with strictures, 229 patients (the majority having left hepatic duct stricture) underwent hepatectomy. Of the 179 patients in the non-hepatectomy group, 30 patients (16.8 per cent) had a long-segment stricture. In the non-hepatectomy group, 104 patients (including the 30 cases of long-segment stricture) received intrahepatic biliary dilatation therapy in addition to the usual treatment. Another 65 patients in the non-hepatectomy group underwent surgery without subsequent biliary dilatation because of poor compliance or other associated disease.

The presence of intrahepatic biliary stricture was determined by preoperative cholangiography, either endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography and, sometimes, postoperative T tube cholangiography. Cases with extrahepatic biliary strictures were excluded. Long-segment biliary stricture is defined as a stenotic segment of the intrahepatic bile duct > 1.5 cm on the cholangiogram. After complete clearance of calculi and apparently successful biliary dilatation in the 30 patients with long-segment biliary stricture, 20 patients underwent intrahepatic stenting (group 1). The other ten patients refused postdilatation stenting (group 2). The status of strictures in group 1 patients was comparable to that in group 2 patients. These patients refused stenting because they were unwilling to have an internal-external stent for 6 months.

Intrahepatic biliary balloon dilatation therapy usually began at least 3-4 weeks after surgery. The track was dilated to 16-24 Fr in two successive sessions with a 3-day interval, usually with the Amplatz renal dilator (Cook, Bloomington, Indiana, USA). Dilatation of the long-segment intrahepatic biliary stricture was then performed with the Dotter angioplasty balloon dilator (Cook). Usually, the balloon used

was 6–8 mm in diameter and 4 cm in length. In some difficult cases, double-balloon dilatation was necessary to obtain an adequate diameter of the stenotic duct. Multiple sessions of dilatation and manipulations were usually necessary to minimize the patient's pain, to prevent prolonged radiation exposure and to obtain the patient's tolerance and acceptance. Stone extraction was simultaneously or subsequently undertaken by basket catheters, biliary spoons or biliary forceps during repeated dilatations. Repeat selective cholangiography and cholangioscopy were performed to evaluate the result of stone clearance and biliary dilatation.

After successful dilatation of the stricture, a Silastic internal–external biliary stent catheter (Cliny cholangioenterotube; Create Medic, Yokohama, Japan) was inserted into the long-segment stricture site (Figure 1). The diameter of the stent varied from 8 to 12 Fr, depending on the stricture location. The access route of the 22 stents in the 20 patients in group 1 included a matured T tube track (five patients), the percutaneous transhepatic biliary drainage track (14 patients), the jejunal limb of a hepaticojejunostomy (two patients), and a fistula (one patient). Two stents were placed in each of two patients and one stent in the other 18 patients. These soft stents were inserted and changed (if malpositioned or blocked) with the aid of a guidewire under fluoroscopic guidance. The cap on the external end of the stenting catheter was closed. The stents were not flushed regularly unless they were blocked (this occurred in three patients). The stent was removed after the improved diameter of the strictured ducts had been demonstrated by serial cholangiography and cholangioscopy (Figure 2).

The duration of stenting varied from at least 6 months to 12 months. If follow-up cholangiography or cholangioscopy at 6 months revealed that the duct diameter of the long-segment stricture had increased but not to the same size as the neighbouring non-stenotic duct, this was defined as a partial success and stenting for a longer period (usually 6 months or more) was indicated. If the post-stenting diameter had not increased at all, the stricture was redilated and subsequently restented. If the stents became blocked, the external cap was opened to establish external biliary decompression, and the stents were flushed with normal saline. After treatment, both the group 1 and group 2 patients were followed up regularly with clinical assessment, periodic abdominal ultrasonography (every 1–2 months) and cholangiography every 6 months to detect recurrence of the stones or the stricture.

The Mann–Whitney *U* test, Student's *t* test, Fisher's exact test,



Figure 1 Postdilatation stenting (arrow) of a long-segment stricture

Table 1 Details of patients having a stent (group 1) and no stent (group 2)

	Group 1 (n = 20)	Group 2 (n = 20)	
Median age (years)	44	45	n.s.
Sex ratio (M:F)	8:12	5:5	n.s.
Secondary biliary cirrhosis	6 (30)	4 (40)	n.s.
Multiple biliary operations	12 (60)	5 (50)	n.s.
Site of stricture			
Right	16 (80)	7 (70)	n.s.
Left	2 (10)	3 (30)	n.s.
Bilateral	2 (10)	0 (0)	n.s.
Location of stricture			
Primary convergence	4 (18)	2 (20)	n.s.
Secondary convergence	16 (73)	7 (70)	n.s.
Tertiary or beyond	2 (9)	1 (10)	n.s.
Median follow-up (months)	50	32	n.s.

Values in parentheses are percentages. n.s., Not significant

Kaplan–Meier method and log rank test were used for statistical analysis.

Results

The demographic data of the two groups were similar (Table 1). During intrahepatic biliary stenting in group 1, the main complications (Table 2) were stent dislodgement in one patient, haemobilia in two patients, cholangitis in two cases and intrahepatic abscess in one. Blockage of stents was found in the latter three patients with time lapses of 3, 4 and 12 months, respectively. The intrahepatic abscess developed in a 50-year-old man with secondary biliary cirrhosis after 1 year of stenting. He underwent a second 6 months of stenting because of poor improvement of a long-segment stricture in the right hepatic ducts. In spite of active management with stent removal, broad-spectrum antibiotics and urgent percutaneous catheter drainage of the abscess, the patient succumbed rapidly. Acute cholangitis in the other two patients was easily controlled with broad-spectrum antibiotics and opening the cap of the external drainage for biliary decompression and flushing with normal saline.

All patients had some improvement in the appearance of the stricture. Five patients underwent restenting for 3 more months because of partial success at the end of 6 months. During the post-stenting follow-up, recurrence of biliary stricture with cholangitis was found in three patients with time lapses of 20, 30 and 42 months. Stone recurrence was detected in two patients. One patient with secondary biliary cirrhosis died from sepsis and hepatic failure. The other two patients with recurrent stricture and cholangitis survived after treatment with percutaneous transhepatic biliary drainage with subsequent biliary redilatation and restenting for 6 more months. The cumulative probability of resticture in group 1 was 5 per cent at 1 year, 10 per cent at 2 years, 15 per cent at 3 years and 21 per cent at 4 years. In group 2, resticture developed in eight patients with a time lapse of 4, 6, 8, 12, 18, 24, 28 and 30 months. Redilatation was undertaken in these cases. The cumulative probability of resticture at the same stenotic site was 60 per cent at 1 year, 80 per cent at 2 years, and is likely to approach 100 per cent at 3 years. Patients who underwent stenting required fewer redilatations than those who underwent dilatation only. In group 2, recurrent cholangitis occurred in all patients who had recurrence of the stricture, and stone recurrence was detected in six patients. There was a statistically significant difference ($P < 0.003$) between group 1 and group 2 in the cumulative probability of biliary resticture.

Discussion

Intrahepatic biliary stricture is a major cause of treatment failure for hepatic duct stones and is also the main cause of



Figure 2 **a** Long-segment intrahepatic biliary stricture with postoperative retained stones in multiple subsegmental ducts. **b** Balloon dilatation of a subsegmental bile duct. **c** Stone extraction with basket catheter after dilatation. **d** Increased diameter of the strictured bile duct after postdilatation stenting for 6 months

Table 2 Complications during stenting

Complication	No. of patients	Time (months)	Symptoms	Management*	Outcome
Dislodgement	1	2	Acute cholangitis	Repositioning	Recovered
Haemobilia	2	2	Minor bleeding	Decompression	Ceased
Occlusion	2	3, 4	Acute cholangitis	Flushing	Recovered
	1	12	Intrahepatic abscess	Stent removal, abscess drainage	Died

*All patients received broad-spectrum antibiotics

stone recurrence. Dilatation of the stricture to facilitate stone retrieval is necessary^{1,4,8-16}. Overall, the early results of dilatation in this unit appear satisfactory, with a 95 per cent complete stone clearance rate and an 8 per cent cumulative probability⁴ of resticture at 3 years. Experience in this hospital suggests that the long-segment stricture is the most difficult to treat; the length of the stenosis is more important than the luminal diameter. Because the long-segment stricture differs from the usual short-segment stricture in both prognosis and treatment, we classify it as a separate entity. For the prevention of stricture recurrence, resection is the treatment of choice. However, this is feasible only in strictures of the left side and in some selected strictures on the right. The factors that preclude resection include a history of multiple biliary surgery, coexistence of secondary biliary cirrhosis, long-segment strictures located at the hilum or beyond the secondary convergence of the right hepatic duct, multiple strictures in different segments, and old age. Dilatation then becomes the preferred method of stricture management, and the immediate results are all satisfactory⁴.

The present results show that biliary stenting achieves a good rate of complete stone clearance and avoids the development of recurrent stricture. Stenting of biliary stricture is recommended after dilatation to maintain the result and to prevent restriking. In our experience, there are four advantages to the internal-external stent. First, repeated follow-up cholangiography is available to evaluate the result during the period of stenting. Second, external drainage can easily be established as an initial treatment whenever acute cholangitis recurs. Third, it is easy to exchange or reposition the stent if it becomes dislodged or occluded. Fourth, manipulation with cholangioscopy or repeated biliary dilatation or restenting can easily be performed through the catheter track. The possible adverse effects of biliary stenting consist of dislodgement, haemobilia, cholangitis and intrahepatic abscess. Two of 20 patients died during follow-up: one from a complication of stenting and one from recurrent stricture.

There is still controversy regarding the duration of stenting. Some authors favour a longer period of stenting of up to 1 year while some suggest 2-4 months. In our experience⁴, restenting is usually necessary if the original stenting lasts for only 2 or 4 months. Although we recommend that the period of stenting be for at least 6 months, 25 per cent (five of 20) and 10 per cent (two) of our stented patients needed 9 and 12 months, respectively, because of only partial improvement of the long-segment stricture after 6 months. Whether prolonged transhepatic tube retention will result in late sequelae is not clearly known. Foreign body reaction and infection may occur. One patient developed an intrahepatic abscess, probably related to the long retention of the stent. Radiography showed a communication between the abscess and the stenotic bile duct containing the stent. Haemobilia occurred in two of our stented

patients who had a long history of repeated cholangitis and secondary biliary cirrhosis. We attribute their haemobilia to a combination of periductal hypervascularity associated with chronic cholangitis and intrahepatic arteriovenous shunting associated with coexistent secondary biliary cirrhosis^{1,2,4}. Whether prolonged stent retention may contribute to peritubal neovascularization and the development of haemobilia is not clearly known.

We recommend that in selected patients with complicated hepatolithiasis with long-segment biliary strictures, intrahepatic biliary stenting after dilatation is a necessary and effective adjunctive management.

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Comparison between diploid and aneuploid hepatocellular carcinomas: a flow cytometric study

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Nuclear DNA content of hepatocellular carcinoma (HCC) was estimated by flow cytometry after hepatic resection in 91 patients during the past 5 years. There were 53 diploid and 38 aneuploid tumours. Clinicopathological features were compared retrospectively between the patients with diploid and those with aneuploid HCC. DNA ploidy did not show any correlation with age, sex, alcohol abuse, hepatitis B virus, serum α -fetoprotein level or underlying liver disease. Histopathologically, the incidence of HCC < 2 cm in diameter tended to be higher in the diploid group but no difference was seen for large tumours (> 5 cm). The grade of tumour differentiation also tended to be higher in this group of small HCC. The ploidy pattern did not influence the rate of capsule or daughter nodule formation, or venous invasion. There were no significant differences in survival rate or in the incidence and time of intrahepatic tumour recurrence between the two groups. This study may indicate that nuclear DNA ploidy is not a particularly predictive factor for the surgical treatment of HCC.

Hepatocellular carcinoma (HCC) is one of the most malignant human tumours and its prognosis without treatment is dismal¹. Hepatic resection is the procedure of choice, but the resectability rate is low owing to a high incidence of associated cirrhosis of the liver, rapid spread of the tumour in the entire liver, or possibly multicentric carcinogenesis². In addition, the rate of intrahepatic tumour recurrence is very high even after curative resection of small HCC complicating cirrhosis³⁻⁵. Surgery alone appears to have limited potential for better therapeutic results.

Several prognostic factors have been proposed after surgical resection of HCC. The following are reported to be favourable: low serum α -fetoprotein (α -FP) level, female sex, absence of cirrhosis, small tumour size, presence of a capsule and absence of androgen receptors⁶. Recent evidence from various malignant tumour studies has suggested that the estimation of DNA content may be useful in predicting the prognosis. Several investigators have also estimated nuclear DNA content of HCC by cytophotometric methods^{7,8} or by flow cytometry^{9,10}, and have compared the clinicopathological features of diploid and aneuploid tumours. These authors have shown conflicting results and there is still controversy about whether or not the ploidy of HCC is a useful predictor of survival.

In the present study, nuclear DNA content of HCC in 91 patients who had undergone hepatectomy was measured. This has allowed a retrospective assessment of the effect of ploidy on the clinicopathological features and prognosis.

Patients and methods

From April 1986 to March 1991 the nuclear DNA content of HCC was estimated by flow cytometry after hepatic resection in 91 consecutive patients without preceding chemotherapy or radiotherapy. Clinicopathological details of these patients were compared retrospectively according to DNA ploidy. Histological diagnosis of HCC and associated parenchymal disease of the liver was made in all cases. Liver cirrhosis was defined according to the criteria of Anthony *et al.*¹¹. Child's classification was used to evaluate the grade of hepatic dysfunction¹². Histological type of the tumour was diagnosed by World Health Organization criteria, and the grade of tumour differentiation defined according to the system of Edmondson and Steiner¹³. When the tumour was composed of areas of different differentiation, the

highest grade was used. Serum levels of hepatitis B virus markers and α -FP were measured by radioimmunoassay.

Flow cytometry

Fresh frozen tissues (49 patients) or paraffin-embedded materials (42 patients) were used. Tumour tissue was frozen in liquid nitrogen immediately after hepatic resection and stored at -170°C until analysis. Approximately 200 mg frozen tissue was minced into pieces of 1 mm³. The minced tissue was mixed in 5 ml 0.1 per cent Triton X-100 (Sigma, St Louis, Missouri, USA), shaken, and then filtered through 40- μm nylon mesh. The filtered solution was centrifuged and the sediment containing nuclei was stained with 0.05 mg/ml propidium iodide (Calbiochem, San Diego, California, USA) and 0.02 mg/ml RNase A (Sigma). After refiltration through 40- μm nylon mesh, nuclear DNA content was measured with a FACS-CAN (Becton-Dickinson, Mountain View, California, USA).

For DNA analysis from paraffin-embedded materials, sections of 50 μm were prepared, cleared of paraffin, rehydrated and digested overnight in trypsin solution (Difco, Detroit, Michigan, USA) containing spermine hydrochloride (Sigma) in a shaking waterbath at 37°C . The resulting nuclear suspension was vortexed, filtered through 40- μm nylon mesh, pelleted, stained with propidium iodide as above, and analysed for DNA content with the FACS analyser.

There were three cases (two paraffin-embedded and one fresh material) in which an adequate analysis of DNA content was impossible, and these were excluded from the study.

Interpretation of DNA histogram

Only samples with at least two separate G0/G1 peaks were considered aneuploid¹⁴. If there was a single G0/G1 peak, the tumour was considered to be diploid. DNA tetraploidy was defined according to a threshold peak size; this was 15 per cent for fresh materials and 20 per cent for paraffin-embedded materials¹⁵. The DNA index was calculated from the ratio of channel numbers of the aneuploid and diploid peaks¹⁴. The coefficient of variation was obtained for all G0/G1 peaks as well as aneuploid peaks.

Statistical analysis

Statistical comparisons were carried out with Student's unpaired *t* test and the χ^2 test. All data in the tables are shown as actual numbers of patients or mean (s.d.). Cumulative survival rates were obtained by the Kaplan-Meier method.

Results

DNA ploidy

Fifty-three patients had HCC of diploid pattern and 38 patients had aneuploid tumours. Among 38 patients with aneuploid HCC, the DNA index was <1.5 in 15. Tetraploid tumours were found in three cases and these were included in the aneuploid group. The incidence of aneuploid tumours was no different between the paraffin-embedded (17 of 42) and fresh (21 of 49) materials.

Clinical background

Preoperative clinical data were compared between the patients with diploid HCC and those with aneuploid tumours (Table 1). There were no differences in age distribution, sex ratio, duration of underlying hepatic disease and incidence of alcohol abuse. The incidence of cirrhosis and distribution of Child's grades were similar in the two groups. Hepatitis B virus markers also showed no difference. Patients with normal serum α -FP levels were seen more frequently in the diploid group but this was not statistically significant.

Hepatic function

Results of preoperative liver function tests are summarized in Table 2. No significant differences were observed between the two groups.

Table 1 Patient details

	Diploid (n = 53)	Aneuploid (n = 33)
Mean(s.d.) age (years)	60.6(8.5)	62.1(8.5)
Sex ratio (M:F)	42:11	29:9
Mean(s.d.) duration of liver disease (years)	8.4(10.4)	6.4(7.0)
Alcohol abuse		
Yes	19	10
No	34	28
Liver cirrhosis		
Yes	36	31
No	17	7
Child's grade		
A	34	26
B	17	9
C	2	3
Hepatitis B virus		
HBeAg positive	2	2
HBsAg positive	14	10
Anti-HBs positive	18	15
Anti-HBe positive	37	28
Serum α -fetoprotein (ng/ml)		
<20	19	9
21–400	26	19
>400	8	10

Table 2 Preoperative liver function tests

	Diploid (n = 53)	Aneuploid (n = 38)
AST (units/ml)	83(54)	75(48)
ALT (units/ml)	76(60)	71(42)
Lactic dehydrogenase (units/ml)	364(120)	367(108)
Bilirubin (μ mol/l)	12.6(5.8)	13.3(8.7)
Albumin (g/l)	37.7(4.9)	36.3(4.7)
Cholesterol (g/l)	1.46(0.30)	1.56(0.35)
ICG R_{15} (%)	23.5(14.5)	25.1(12.5)
BSP R_{30} (%)	27.8(12.0)	28.6(9.5)

Values are mean(s.d.). AST, aspartate aminotransferase (normal range 0–37 units/ml); ALT, alanine aminotransferase (normal range 3–32 units/ml); ICG R_{15} , indocyanine green retention rate at 15 min (normal range 0–10 per cent); BSP R_{30} , bromsulphthalein retention rate at 30 min (normal range 0–10 per cent).

Table 3 Operative and postoperative data

	Diploid (n = 53)	Aneuploid (n = 38)
Liver resection		
Minor	40	27
Major	13	11
Postoperative chemotherapy*		
Yes	28	14
No	22	19
Mean(s.d.) follow-up (months)	29.4(14.9)	30.4(17.6)
Recurrence*		
Yes	24	18
No	26	15
Mean(s.d.) time of recurrence (months)	14.4(11.4)	14.8(11.5)

*Operative deaths are excluded

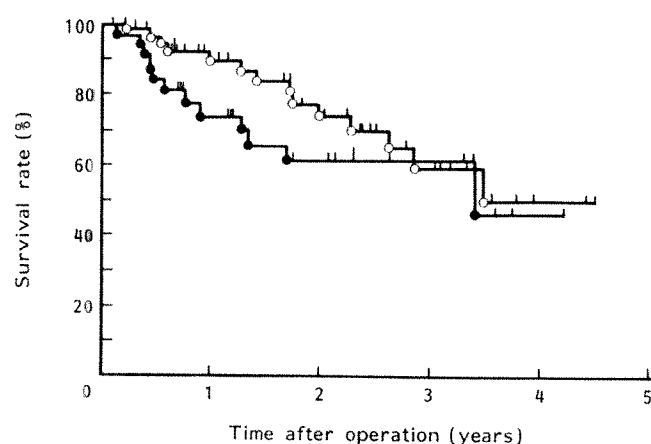


Figure 1 Cumulative survival curves for patients with diploid (n = 50: Δ , survived; $\bullet$, died) and aneuploid (n = 33: Δ , survived; $\bullet$, died) hepatocellular carcinoma after hepatic resection. Operative deaths were excluded; there was no statistically significant difference between the two groups

Perioperative data

There was no difference in the extent of hepatic resection. In this report, minor hepatectomy was defined as a resection of less than two segments as described by Couinaud¹⁶. The operative mortality rate was 6 per cent (three patients) in the diploid and 13 per cent (five patients) in the aneuploid group. Postoperative chemotherapy with epirubicin or 5-fluorouracil derivatives was given to 42 patients who survived surgery. The use of adjuvant chemotherapy did not differ significantly between the two groups (Table 3).

Tumour recurrence

The follow-up was similar between the groups. There were no significant differences in either intrahepatic recurrence rate or time of the recurrence (Table 3).

Survival rate

Figure 1 shows the survival curves of both groups after exclusion of operative deaths. No statistical difference was observed between the diploid and aneuploid groups. In 33 patients with aneuploid HCC who survived hepatic resection, the DNA index did not influence the survival rate (Figure 2).

Histopathology

The incidence of HCC <2 cm in diameter tended to be higher in the diploid group, but tumours >5 cm were found equally in both groups. A lower rate of capsule formation and a higher incidence of daughter nodules and venous invasion were noted in the aneuploid group, but these were not statistically significant. The grade of tumour differentiation tended to be

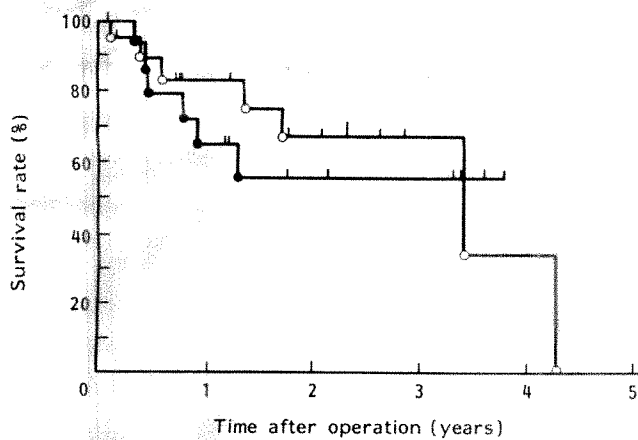


Figure 2 Cumulative survival curves for patients with aneuploid hepatocellular carcinoma with a DNA index ≥ 1.5 ($n = 19$: Δ , survived; $\circ$, died) or < 1.5 ($n = 14$: Δ , survived; $\bullet$, died). Operative deaths were excluded; there was no statistically significant difference between the two groups

Table 4 Histopathological data

	Diploid ($n = 53$)	Aneuploid ($n = 38$)
Tumour size (mm)		
≤ 20	6 (11)	1 (3)
21–50	32 (60)	27 (71)
51–100	11 (21)	8 (21)
> 100	4 (8)	2 (5)
Capsule formation		
Yes	38 (72)	24 (63)
No	15 (28)	14 (37)
Daughter nodules		
Yes	22 (42)	18 (47)
No	31 (58)	20 (53)
Venous invasion		
Yes	19 (36)	18 (47)
No	34 (64)	20 (53)
Edmondson's grade		
I	4 (8)	0 (0)
II	34 (64)	16 (42)
III	13 (25)	21 (55)
IV	2 (4)	1 (3)
Liver disease		
Cirrhosis	36 (68)	31 (82)
Chronic hepatitis	17 (32)	5 (13)
None	0 (0)	2 (5)

Values in parentheses are percentages

higher for the diploid tumours; in particular, HCC of Edmondson grade I was found only in the diploid group. There was no difference in underlying liver disease (Table 4).

Discussion

In order to design effective therapy against a malignant tumour, it is of crucial importance to know its biological behaviour. In HCC, which is one of the most malignant human tumours, several biological factors have been suggested to represent the grade of malignant potential or to predict the patient's prognosis. It has been suggested that a lesser malignant potential and a better prognosis may be predicted by low serum α -FP level, small tumour size, absence of lymph node metastasis or vascular invasion, capsule formation and high histological differentiation.

During the past decade, much evidence has suggested that in various malignant tumours the biological behaviour is reflected by nuclear DNA content. Diploid tumours may be less malignant and may carry a better prognosis than aneuploid or non-diploid ones. Several techniques are available at present

to estimate nuclear DNA content. Nevertheless, there are only a few investigations that have reported on the significance of DNA ploidy in the management of HCC.

Using a cytophotometric method, Kuo *et al.*⁷ investigated the DNA content of aspirated HCC cells in 54 patients. The modal DNA value was related only to serum α -FP level. HCC in those with higher α -FP levels contained more hyperploid cells. DNA ploidy had no correlation with age, hepatitis B virus, tumour size or histological grade. Almost the same result was obtained by Chen *et al.*¹⁰ who studied resected material by flow cytometry. On the other hand, two Japanese groups found a correlation between DNA ploidy and age, tumour size, Edmondson's grade, venous invasion and intrahepatic metastasis^{8,9}. Fujimoto *et al.*⁹ had a clearly improved survival rate after hepatic resection in patients with diploid HCC compared with those with aneuploid tumours. They also showed that aneuploid HCC with a DNA index < 1.5 gave the worst prognosis. Other groups, however, have not observed such a significant difference in survival rate between diploid and aneuploid tumours^{8,10}.

In the present study there were no significant differences between the patients with diploid and aneuploid HCC with regard to age, sex, duration and grade of underlying liver disease, hepatitis B virus profile and serum α -FP level. Histopathologically, the incidence of very small (< 2 cm) and highly differentiated (Edmondson grade I) HCC tended to be greater in the diploid HCC group. The DNA pattern did not correlate with capsule formation, intrahepatic metastasis or venous invasion. Also, the ploidy pattern did not influence the survival rate or the incidence and time of tumour recurrence after hepatic resection.

Thus, the clinical significance of nuclear DNA ploidy in HCC remains controversial. The present results suggest that the estimation of DNA content is not particularly useful in the surgical management of this tumour. One important reason for this might be that intrahepatic recurrence frequently occurs even after curative resection of the primary tumour^{3–5}. In other words, irrespective of the DNA ploidy of the primary HCC, new tumours of multicentric origin can frequently develop in the residual liver^{17–19}. In the present study, this might have nullified DNA ploidy as a prognostic factor of HCC, particularly for tumour recurrence and survival.

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Case report

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Bilateral pancreaticopleural fistulae treated by distal pancreatectomy

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Pancreaticopleural fistulae are a serious complication of pancreatitis. In most cases surgical therapy cannot be avoided. A patient is reported with bilateral pancreaticopleural fistulae complicating chronic alcoholic pancreatitis. Distal pancreatectomy was successfully performed after the patient failed to respond to a 10-day course of octreotide (Sandostatin; Sandoz, Uden, The Netherlands) and an unsuccessful attempt to place a stent in the stenotic pancreatic duct.

Case report

A 50-year-old man was admitted with a 6-day history of painful erythema on both legs. Over the past 6 months he had lost about 30 kg in body-weight and become progressively tired. He smoked 30 to 40 cigarettes and drank 2 litres of spirits per day. Clinical examination revealed signs of chronic bronchitis, an enlarged liver, and erythema nodosum lesions on both legs. Neither jaundice nor ascites was present.

The serum amylase concentration was >7000 units/l, but results of all other blood tests were normal. Ultrasonography revealed a pseudocyst in the pancreas and some ascites. Chest radiography showed pneumonia in the left lower lobe. Biopsy of the erythema showed metastatic fat necrosis.

Initial treatment consisted of antibiotics, H₂-receptor antagonists and total parenteral nutrition. Computed tomography (CT) 22 days after admission showed a pseudocyst in the head of the pancreas, ascites, and bilateral pleural effusions. Endoscopic retrograde cholangiopancreatography (ERCP) revealed a stenosis in the middle portion of the pancreatic duct immediately behind which was a 7-cm pseudocyst.

Five weeks after admission the patient became acutely dyspnoeic.

Chest radiography showed a right-sided pleural effusion, from which 2 litres of fluid was aspirated, rich in amylase (446 600 units/l). Disappearance of the pseudocyst on ultrasonography suggested the development of a pancreaticopleural fistula, which was confirmed by a second ERCP procedure (Figure 1). After another 4 litres of amylase-rich fluid had been evacuated from the chest through a tube drain, subcutaneous octreotide (600 µg) was administered. The volume of fluid drained decreased to 100 ml during the next day but increased thereafter to 800 ml/day. An endoscopic attempt to drain the distal pancreatic duct was prevented by the severe duct stenosis (Figure 1). High output continued from the right chest drain (approximately 600 ml/day) and subsequently from a left chest drain (approximately 1000 ml/day) despite continuous octreotide therapy (600 µg/day).

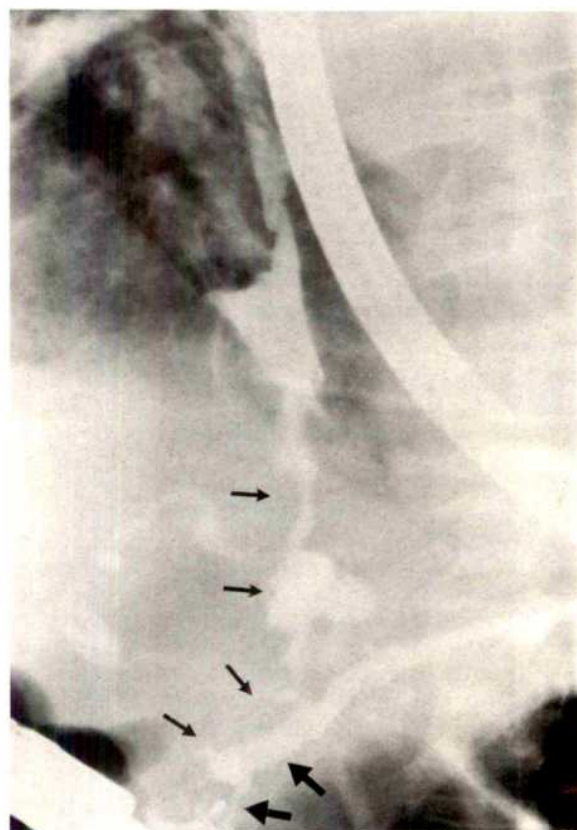


Figure 1 Endoscopic retrograde cholangiopancreatogram showing stenosis in the pancreatic duct with a dilated segment upstream (large arrows). The small arrows indicate the fistular track

Seven weeks after admission, distal pancreatectomy was performed together with cholecystectomy and splenectomy. The postoperative recovery was uneventful. In the resected specimen, consisting of the neck, body and tail of the pancreas, pathological examination revealed a fistula between the cystic dilated main pancreatic duct and the upper border of the gland. The pancreatic tissue had a firm, fleshy appearance and histological examination revealed severe chronic pancreatitis with atrophy of at least 25 per cent of the exocrine tissue.

At follow-up 6 months later the patient was found to have developed diabetes mellitus and peripheral neuropathy secondary to alcohol abuse.

Discussion

Pancreaticopleural fistula is a rare complication of chronic pancreatitis. The incidence may be between 1 and 4 per cent of patients with pancreatic pseudocysts, but is probably <0.5 per cent overall in those with chronic pancreatitis¹. The aetiological factor is alcohol abuse in 75 per cent of cases. In a review of 96 patients¹, 60 per cent had pulmonary symptoms without abdominal symptoms and only half had a known history of pancreatitis. Although the patient discussed initially developed a right pleural effusion, in 70 per cent of cases the left side is affected first¹.

After aspiration of pleural fluid and measurement of its amylase content to confirm the diagnosis, CT and ERCP are necessary to visualize the pancreatic duct, possible pseudocysts and the location of the fistulae. Initial treatment involves total parenteral nutrition and drainage of the effusion by repeated thoracocentesis (or continuously by a chest drain).

Although octreotide or its analogues can reduce fistula output^{2,3} by inhibiting exocrine pancreatic secretion, this

treatment is more successful in external than in internal fistulae that do not drain to the gut^{4,5}. In this case, the stenosis in the pancreatic duct prevented proper drainage from the distal gland and probably explained the transient nature of the response to octreotide.

Surgical treatment should be undertaken¹ if medical therapy is not successful within 2 weeks. Decompression of the stenotic or obstructed pancreatic duct and excision of the obstructed pancreas have been recommended⁵. Among 96 patients, medical therapy was successful in 41 per cent and failed in the remainder. Sixty-six patients were treated surgically, the most common procedure (31 per cent) being distal pancreatectomy¹.

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Announcement

The Cutlers' Prize

A development in minimally invasive surgery has won the Cutlers' Prize. The award has been made to Mr A. W. Majeed of the University Department of Surgery, Royal Hallamshire Hospital, Sheffield, UK, for the development and clinical testing of a new instrument that allows gallstones to be removed under direct vision using local or regional anaesthesia.

Mr Majeed's invention, named the Sheffield cholecystoscope, is an important advance in terms of safety and effectiveness, particularly for patients who are elderly and for whom general anaesthesia is not recommended, and for younger patients who wish to retain a functioning gallbladder. It consists of a double tube that is inserted into the abdomen through a small incision. The surgeon can visualize structures through the cholecystoscope and identify the gallbladder. Suction applied through the cholecystoscope creates a vacuum that secures the instrument to the gallbladder with a perfect seal, preventing bile leakage. The gallbladder is incised, the stones removed under direct vision, and the gallbladder washed out to prevent stone recurrence. The patient can usually be discharged the next day. The instrument is simple in design and easy to use.

The Cutlers' Prize is awarded annually by the livery company for an outstanding advance in the design of surgical or medical instrumentation and comprises a silver medal and the sum of £1000. The Prize is administered jointly with the Association of Surgeons of Great Britain and Ireland and the winner chosen by a committee chaired by the President of The Royal College of Surgeons of England. Further details may be obtained from: Mr P. Baker, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK.

Vascular inflow exclusion and hepatic resection ($P < 0.05$),

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Seventy-nine patients undergoing hepatic resection without manipulation of the vena cava were divided into three groups. Group 1 consisted of 32 patients in whom hepatic hilar vascular exclusion was not performed. Group 2 (20 patients) had vascular inflow exclusion performed at the operative site only (right or left unilateral exclusion). Group 3 (27 patients) had total inflow exclusion during hepatic resection. There were no significant differences between the groups in blood loss or blood transfusion requirement. On the third day after operation, the serum glutamic-pyruvic transaminase level in group 3 was significantly higher than that in group 1 ($P < 0.01$). Vascular inflow exclusion may not be essential for successful hepatic resection.

The technique of hepatic resection has recently been standardized and the operative mortality rate has decreased¹. This may be caused by a decrease in operative blood loss resulting from better knowledge of the intrahepatic anatomy² and the use of ultrasonic surgical aspirators³. Attempts have been made to reduce intraoperative bleeding and equipment has been designed to this end⁴⁻⁹. The latest procedure for hepatic resection includes vascular inflow exclusion at the hilus¹⁰. The ultrasonic surgical aspirator is so effective, however, that vascular exclusion and other instruments to decrease intraoperative blood loss may be unnecessary. This study examines the requirement for hepatic hilar vascular exclusion when hepatectomy is performed using an ultrasonic surgical aspirator.

Patients and methods

Seventy-nine patients undergoing hepatic resection were divided into three groups. Patients who had surgery involving the inferior vena cava were excluded. All hepatic resections including segment VII or VIII¹¹ were performed by laparophrenothoracotomy¹² and others were carried out during laparotomy. Patient details are summarized in Table 1.

Thirty-two patients (group 1) had no vascular hilar exclusion. Twelve of these patients had liver cirrhosis. When segmentectomies² or partial resections were performed in this group, no vascular exclusion was used. Lobectomies and hepatectomies² were performed without vascular exclusion after division of both the portal vein branch and the hepatic artery at the operative site (Figure 1a).

Twenty patients (group 2, 17 men and three women) had vascular inflow exclusion only on the vessels at the operative site (right or left side unilateral exclusion). Hilar vascular exclusions were performed using two 3-Fr Nelaton catheters around the vessels which were grasped by Bulldog forceps (Figure 1b). When central bisegmentectomy¹³ was performed vascular occlusion of the right and left sides was carried out sequentially.

Group 3 (27 patients) had complete occlusion of inflow to the liver. All patients in this group with hepatocellular carcinoma had liver cirrhosis (Table 1). Occlusion of the portal trunk and hepatic artery was carried out in the same manner as in group 2 (Figure 1c), or by using an intestinal clamp wrapped in rubber tubing to avoid injury to the surrounding tissue (Figure 1d).

A period of 10 min of occlusion for patients with cirrhosis or 15 min for those without was followed by 5 min of blood flow. This sequence was repeated until hepatic dissection was complete. Intraoperative ultrasonography was performed during the declamping period.

Dissections were performed using an ultrasonic surgical aspirator (Sonotec; Mochida, Tokyo, Japan) and an electric coagulator (Mera NS-8000; Yamaguchi Ika Seisakusho, Tokyo, Japan). Blood vessels and bile ducts > 1 mm in diameter were ligated with 3/0 silk. Vessels < 1 mm were coagulated. Other bleeding vessels were occluded with 3/0 non-absorbable ligatures on atraumatic needles.

Blood was taken on the morning of the operation and 1, 3 and 7 days after operation and analysed for: total bilirubin, lactate dehydrogenase (LDH), and serum glutamic-oxaloacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT).

Student's t test, Wilcoxon's test, χ^2 test, one-way analysis of variance (ANOVA), or the Kruskal-Wallis H test was used for statistical analysis.

Results

There were no significant differences in sex, distribution of pathology or the proportion of patients with liver cirrhosis among the three groups or between any two groups (χ^2 test). There were no significant differences in age or the mean 15-min indocyanine green clearance test result among the three groups by the Kruskal-Wallis H test or between any two groups using Student's t test. The three groups were therefore demonstrated to be clinically equal.

Operative details are shown in Table 2. In group 1, five right lobectomies, eight hepatectomies, one central bisegmentec-

Table 1 Patient details

Group	No. of patients	Sex ratio (M:F)	Mean (range) age (years)	Pathology					Mean (range) ICGR ₁₅ (%)
				Hepatocellular carcinoma	Liver metastasis	Bile tract cancer	Other	Liver cirrhosis	
1	32	24:8	58.0 (42-76) [54.5-61.5]	13	12	3	4	12	13.5 (2.0-50.0) [9.4-17.6]
2	20	17:3	59.7 (40-74) [55.3-64.1]	11	8	1	0	9	14.5 (4.5-35.0) [9.5-19.6]
3	27	19:8	58.7 (40-77) [54.8-62.5]	14	8	4	1	14	20.3 (2.5-51.2) [16.0-24.6]
Total	79	60:19	58.7 (40-77)	38	28	8	5	35	16.1 (2.0-51.2)

Values in square brackets are 95 per cent confidence intervals. ICGR₁₅, 15-min indocyanine green clearance test. No significant differences were found between groups for any parameter (see text for statistical details)

segmentectomies with or without partial resection, lobectomies and two combined partial resections were performed. Nineteen patients did not require blood transfusion. Total gastrectomy with partial transverse colectomy was necessary for one patient who had hepatocellular carcinoma complicated by a remnant gastric cancer. Sigmoid colectomy

and partial resection of the ileum were necessary for patients with synchronous liver metastases from cancer of the sigmoid colon, and hepatocellular carcinoma complicated by submucosal tumour of the ileum, respectively.

Patients in group 2 underwent one central bisegmentectomy, one right hepatectomy with partial resection, one segmentectomy with subsegmentectomy, five segmentectomies with or without partial resection, two resections of two subsegments, eight subsegmentectomies with or without partial resection, and two combined partial resections (Table 2). Subsegmentectomy is defined as the removal of one of the eight segments defined by Couinaud¹¹. Twelve patients did not require blood transfusion. Sigmoid colectomy was necessary for one patient with hepatic metastases from cancer of the sigmoid colon.

Patients in group 3 underwent one right lobectomy, two left trisegmentectomies, one left hepatectomy, six segmentectomies with or without partial resection, five subsegmentectomies with or without partial resection, and 12 partial resections (Table 2). Fifteen patients required no blood transfusion. Subtotal oesophagectomy, sigmoid colectomy, Hassab's operation¹⁴ with splenectomy, and inguinal herniorrhaphy were necessary for patients with oesophageal cancer with liver metastases, synchronous liver metastases from cancer of the sigmoid colon,

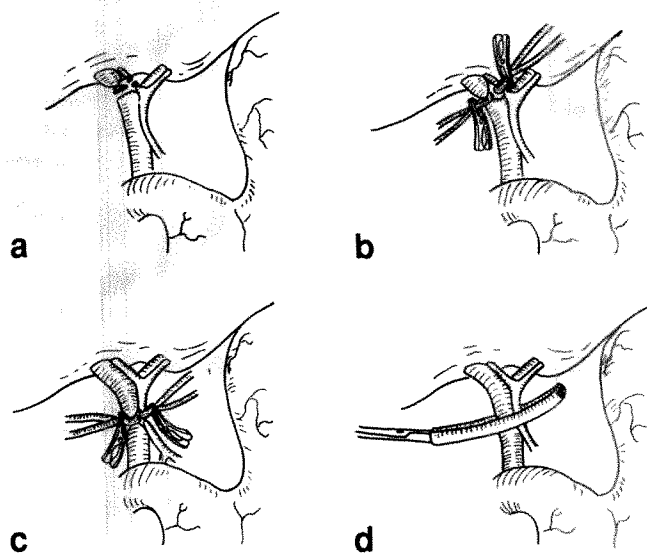


Figure 1 a In group 1, segmentectomies or partial resections were performed without vascular exclusion, and lobectomies or hepatectomies without vascular inflow exclusion after division of both the portal vein branch and the hepatic artery at the operative site. b In group 2, hilar vascular occlusion was performed at the operative site. In group 3, hilar occlusion was performed at the portal trunk and the hepatic artery by using c Nelaton catheters or d an intestinal clamp wrapped in rubber tubing

Table 3 Differences of means of operation time and operative blood loss

	Group 1 versus 2	Group 1 versus 3	Group 2 versus 3
Operation time			
95% confidence interval (min)	-88.4-39.9	-77.9-43.9	-62.5-76.9
F ratio	0.58	0.31	0.043
P	0.50	0.60	0.90
Operative blood loss			
95% confidence interval (g)	-981-1121	-921-1063	-897-899
F ratio	0.018	0.021	7×10^{-6}
P	0.90	0.90	1.00

1 d.f.

Table 2 Operative details

Group	No. of patients	Extent of resection (no. of segments)*				Mean (range) operation time (min)	Mean (range) blood loss (g)	Mean (range) transfusion requirement (units)
		<1	1	2 or 3	≥4			
1	32	5	2	11	14	285 (140-637) [245-325]	1700 (110-10 689) [1085-2316]	1.41 (0-15.0) [0.5-2.3]
2	20	1	9	8	2	309 (130-520) [259-360]	1630 (270-6021) [851-2408]	1.20 (0-11.5) [0-2.4]
3	27	12	5	6	4	302 (90-516) [258-346]	1629 (80-8500) [959-2299]	1.43 (0-9.0) [0.4-2.5]
Total	79	18	16	25	20	296 (90-637)	1665 (80-10 689)	1.36 (0-15.0)

Values in square brackets are 95 per cent confidence intervals. *The eight segments are classified according to Couinaud¹¹. No significant differences were found between groups for operation time, blood loss or transfusion requirement (Student's *t* test and Wilcoxon's test)

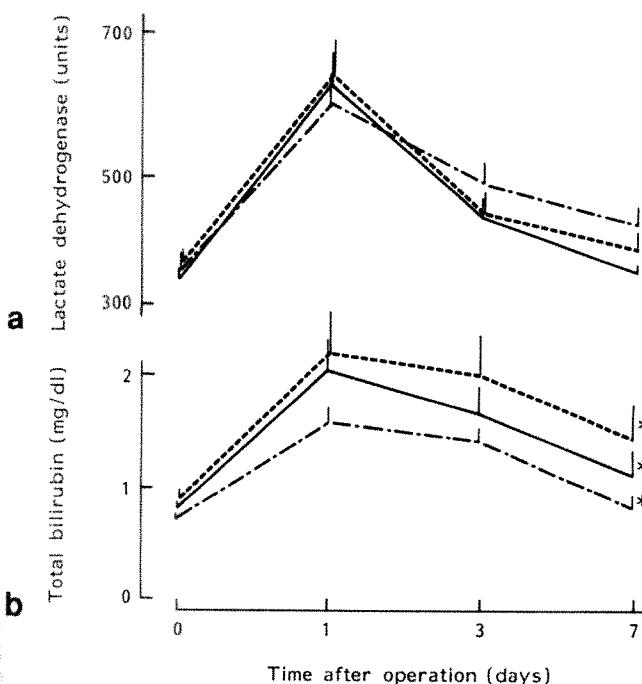


Figure 2 Mean (s.e.m.) levels of a lactate dehydrogenase and b total bilirubin before and after operation. —, Group 1; ---, group 2; ·····, group 3. *P < 0.05 (one-way analysis of variance)

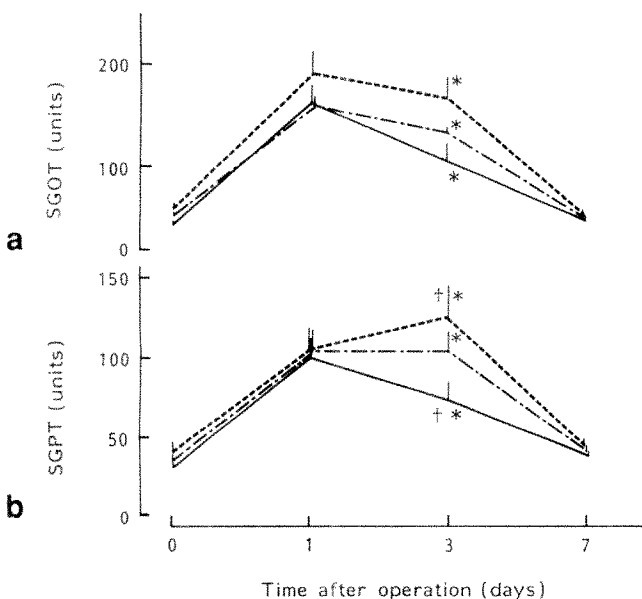


Figure 3 Mean (s.e.m.) levels of **a** serum glutamic-oxaloacetic transaminase (SGOT) and **b** serum glutamic-pyruvic transaminase (SGPT) before and after operation. —, Group 1; ---, group 2; ·····, group 3. * $P < 0.05$ (one-way analysis of variance); † $P < 0.01$ (Student's *t* test)

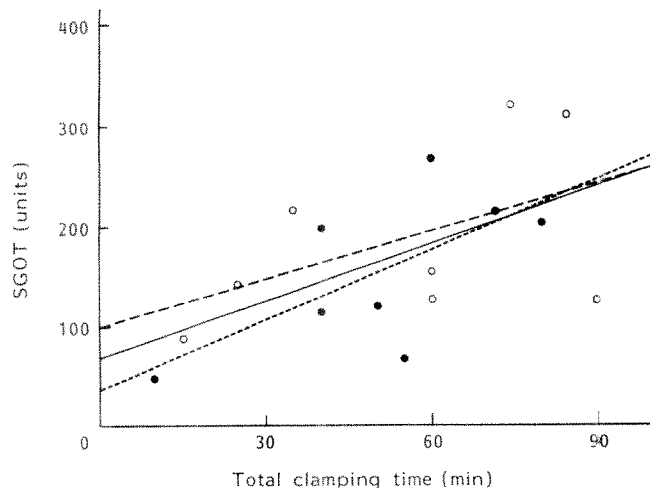


Figure 4 Correlation between total clamping time and mean levels of serum glutamic-oxaloacetic transaminase (SGOT) in group 3 patients on day 1 after operation. ●, Patients with liver cirrhosis (----); ○, patients with no liver cirrhosis (---); —, all patients

hepatocellular carcinoma complicated by gastric varices, and right external inguinal hernia, respectively.

There were no significant differences in mean operation time (F ratio 0.30, 2 d.f., $P = 0.80$), mean blood loss (F ratio 0.015, 2 d.f., $P = 0.99$), and mean blood transfusion requirement (F ratio 0.048, 2 d.f., $P = 0.98$) among the three groups by ANOVA, or between any two groups by Student's *t* test or Wilcoxon's test (Table 2). The 95 per cent confidence intervals, F ratios and P values of differences of means of operation time and operative blood loss are shown in Table 3.

Serial changes in total serum bilirubin, LDH, SGOT and SGPT for each group are shown in Figures 2 and 3.

Patients who underwent total vascular occlusion in the manner shown in Figures 1c and 1d were grouped together because there were no significant differences between them in characteristics, operative details or data obtained before or after surgery.

In Figure 4, the relationship between the total clamping time and SGOT levels of patients in group 3 on the first day after operation is shown. The correlation coefficients overall and for

cirrhotic patients were 0.56 ($P < 0.05$) and 0.6, respectively.

Discussion

The currently accepted, standard technique of hepatectomy is resection using an ultrasonic surgical aspirator¹⁵⁻¹⁷ under temporary inflow occlusion^{10,18-20}. Vascular hilar exclusion has resulted in a reduction in intraoperative blood loss as described by Pringle²¹. Various techniques and instruments have been devised for the purpose of decreasing haemorrhage^{3-10,15-20}. These can be classified into two groups. The first group consists of techniques for the reduction of blood loss by occlusion of hepatic inflow^{10,18-23}. Compression of the hepaticoduodenal ligament is usually performed because it is known²⁴⁻²⁶ that the liver can tolerate normothermic ischaemia for up to 60 min. The other group consists of devices such as clamps and bands to help reduce blood loss from the cut hepatic surfaces⁴⁻⁹. Using these instruments, anatomical liver resection^{10,27} cannot be performed. Consequently, the control of hepatic inflow is performed more frequently than the control of hepatic parenchyma.

The ultrasonic dissector was subsequently developed and applied to hepatic resection¹⁵⁻¹⁷; one advantage is that it can aspirate hepatic parenchyma without affecting vessels and bile ducts. Ligation and division of vessels and bile ducts decreases intraoperative haemorrhage and bile leakage after operation. In addition, coagulation of the hepatic parenchyma reduces blood loss from the surface of the hepatic dissection. The walls of hepatic veins are weaker than those of arteries, portal veins or bile ducts, and care must be taken when using ultrasonic dissection. Inflow occlusion does not prevent bleeding from hepatic veins but if total vascular exclusion, including clamping of the vena cava below and above the liver, is performed²⁸, then blood loss from hepatic veins will decrease. It may be inappropriate to perform caval clamping when hepatic hilar exclusion is not carried out. If the hepatic veins are treated carefully, then haemorrhaging from them will decrease. In the current investigation great care was taken to coagulate bleeders from hepatic parenchyma by electric spray coagulation. The hepatic veins and their branches were ligated diligently during hepatic dissection. As a result, operative time, intraoperative blood loss and blood transfusion requirement in group 1 were no greater than in the other groups.

In group 3, however, changes in liver function after operation were correlated with the total clamping time. Changes in those with or without cirrhosis were almost identical and the disparity in the percentage of patients with liver cirrhosis among the three groups was not significant.

Although the liver can withstand normothermic ischaemia for up to 60 min²⁴⁻²⁶, after operation the mean serum LDH, SGOT, SGPT and total bilirubin levels of group 3 were higher than those of the other two groups. The mean SGPT level of group 3 on the third day after operation was strikingly higher than that of group 1.

Total occlusion of hepatic inflow cannot be thought of as a harmful procedure, because all levels returned to preoperative ranges within 1 week. If hepatic inflow exclusion damages the liver and decreases operative blood loss minimally, this procedure is not essential. Hepatic resection can be performed safely if an ultrasonic surgical aspirator and electric coagulator are used carefully. The data suggest that controlling the hepatic parenchyma is as effective as controlling the hepatic inflow for the purpose of reducing intraoperative blood loss.

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Announcement

Association of Surgeons in Training

Membership of the Association is open to trainees in all the surgical specialties. Applicants should be at least 2 years after Fellowship. It is anticipated that at this year's AGM the constitution will be amended to allow all graduates of the Clinical Surgery in General exam to apply for membership. The Association represents the views of members on all matters relevant to surgical training and has representatives on most of the committees and boards that administer British surgery. Membership is free. If you are not a member please contact the Secretary, Bob Baigrie, 7 Coverley Road, Oxford OX3 7ET, for details of membership, the AGM and the name of your local representative. The next AGM will be held on 23-24 September 1992 in conjunction with the Autumn meeting of the Association of Surgeons of Great Britain and Ireland in Dublin.

R. J. Baigrie

Potential candidates for small bowel transplantation

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The number of potential candidates for small bowel transplantation in the UK is unknown. Potential recipients are those with irreversible small intestinal failure, including those treated with permanent parenteral nutrition. This study of one of the largest groups of patients receiving such nutrition identified ten of 25 adult patients as possible recipients. The remaining 15 were considered unsuitable, mainly because of multiple previous abdominal operations or abscesses. Extrapolation of these data to national figures on the incidence of irreversible small intestinal failure suggests that each year up to 20 new adult patients in the UK might benefit from small bowel transplantation.

Intestinal failure has been defined as an inability to maintain nutrition and/or positive intestinal fluid and electrolyte balance without special measures¹. Patients with small intestinal failure include those with insufficient length of small bowel following surgical resection and those with functional insufficiency secondary to absorption or motility disorders. In most patients, small intestinal failure is reversible after a period of temporary support on parenteral nutrition^{2,3} during which adaptation of the remnant occurs or a problem such as an enterocutaneous fistula is treated. A small group of patients has irreversible small intestinal failure and requires permanent parenteral nutrition for survival⁴. Long-term parenteral nutrition, in both adults and children, is associated with side-effects that include catheter-related sepsis, venous thrombosis and liver failure⁵⁻⁸. There is also a significant mortality rate associated with long-term parenteral nutrition, due to both the underlying disease and complications of therapy^{8,9}.

After surgical resection the residual small bowel undergoes adaptation, principally by villous hyperplasia¹⁰. The ileum has a greater potential for adaptation than the jejunum^{10,11} and the time taken to achieve maximum adaptation^{2,12,13} may exceed 2 years. Factors influencing the success of adaptation include the length of residual disease-free intestine and the presence of the ileocaecal valve, which is believed to help by slowing intestinal transit^{14,15}. The presence of luminal nutrition also facilitates adaptation¹⁶. The minimum length of small intestine necessary for survival and resumption of an enteral diet has not been established¹⁷; case reports exist of patients surviving with an extremely short small bowel¹⁸. However, published series suggest that in infants a minimum of 20 cm of intestine with an ileocaecal valve, or 40 cm without, is necessary for adequate enteral nutrition^{7,14}. Before the availability of parenteral nutrition, few adults achieved long-term survival with <150 cm of small bowel¹⁹. Of the patients with small intestinal failure treated at St Mark's Hospital in the past 10 years, most with >100 cm of residual normal small bowel have been able to return to enteral feeding. The majority of patients who manage to revert to full enteral nutrition²⁰ do so within 2 years.

A small bowel allograft is an alternative to parenteral nutrition for patients with irreversible small intestinal failure. Transplantation was first attempted in humans in the 1960s with appalling results²¹, but since 1988 successful small bowel transplants have been carried out in the USA^{22,23} and Europe²⁴ using newer forms of chemical and biological immunosuppression. Some patients who received small bowel transplants up to 2 years ago are leading relatively normal lives and feeding entirely by the enteral route. Human small bowel transplantation has not yet been reported in the UK, and the purpose of this study was to identify potential candidates.

Patients and methods

The North-East Thames Region was surveyed to find the number of patients receiving permanent parenteral nutrition, the aetiology of their intestinal failure, and their suitability for small bowel grafting. Patients were identified by inspection of the register of patients on parenteral nutrition based at St Mark's Hospital, which is the regional centre for patients with small intestinal failure. In addition, all the hospital pharmacies in the region were contacted to identify further patients receiving parenteral nutrition, and the national register of patients receiving home parenteral nutrition consulted to ensure that no patient had been omitted². For patients being treated for irreversible intestinal failure, hospital notes were reviewed and the responsible consultants interviewed. The consultants' views on the suitability of small bowel transplantation were elicited for each patient.

Results

There were 25 adult patients receiving parenteral nutrition for irreversible small intestinal failure. Twenty-three were based at St Mark's and two at the Royal London Hospital. There were 17 women and eight men aged from 18 to 61 (median 41) years. The patients had been treated at home for 1-10 (median 6) years. There were three children, aged 8, 8 and 2 years, who had been receiving treatment for 5 years, 1 year 8 months, and 1 year 9 months, respectively.

After discussion with the consultants involved, each patient was placed into one of three categories depending on their suitability for transplantation. These are shown in *Tables 1-3*. The reasons given by the consultants for or against transplantation are included. Three of the 25 patients were considered to be good candidates for transplantation and a further seven to be possible candidates. Fifteen patients were thought to be unsuitable. None of the three children was considered suitable for transplantation because they were all managing adequately on parenteral nutrition.

Discussion

The North-East Thames Region has one of the largest UK populations on parenteral nutrition, as St Mark's Hospital is a specialist centre for this group of patients and receives adult patients from the whole of London and much of densely populated south-east England¹. The national register of home parenteral nutrition is kept at Hope Hospital in Manchester², which has the other major concentration of individuals on home parenteral nutrition in the UK. The remaining patients on the national register are treated at 27 separate centres (up to six patients per centre). The register cannot be used to identify potential candidates for transplantation because it does not distinguish between those with permanent and those with temporary small intestinal failure.

Table 1 Possible candidates for small bowel transplantation

Patient no.	Age (years)	Aetiology of small intestinal failure	Anatomy	Duration of home parenteral nutrition (years)	Reason for transplant
1	20	Volvulus	Short bowel, jejunocolic anastomosis	3	Young, fit, little previous surgery
2	25	Volvulus	Jejunocaecal anastomosis	4	Young, fit, little previous surgery
3	32	Total colectomy (for ulcerative colitis), internal hernia causing small bowel infarct	Duodenoanal anastomosis	6	Young, fit, little previous surgery

Table 2 *Possible candidates for small bowel transplantation*

Patient no.	Age (years)	Aetiology of small intestinal failure	Anatomy	Duration of home parenteral nutrition (years)	Reason for caution*
4	51	FAP with desmoids	End duodenostomy	8	Multiple surgery
5	47	SMV thrombosis	Duodenocaecal anastomosis	8	Previous severe pancreatitis with adhesions
6	51	Systemic sclerosis with pseudo-obstruction	Enteroenterostomies and end ileostomy	9	Multiple surgery
7	38	Crohn's disease	Jejunocolic anastomosis	10	Multiple surgery
8	50	Radiation enteritis	End jejunostomy	9	Multiple surgery, irradiation
9	18	Visceral myopathy	Gastroenterostomy, end ileostomy	9	Will stomach empty?
10	37	Crohn's disease	Short bowel, end ileostomy	1	Multiple surgery, dependent children

FAP, familial adenomatous polyposis; SMV, superior mesenteric vein. *Multiple surgery represents more than three laparotomies

Table 3 *Patients considered unsuitable for small bowel transplantation*

Patient no.	Age (years)	Aetiology of small intestinal failure	Anatomy	Duration of home parenteral nutrition (years)	Reason not to transplant*
11	29	Visceral myopathy	Enteroenterostomies, end ileostomy	6	Stomach does not empty
12	54	Crohn's disease	Short bowel, end jejunostomy	9	Multiple surgery, stroke
13	54	Crohn's disease	Short bowel, end ileostomy	8	Multiple surgery with intestinal fistulae
14	50	Pseudo-obstruction	End jejunostomy	6	Second mitral valve xenograft
15	32	Visceral myopathy	Enteroenterostomies, ileorectal anastomosis	8	Multiple surgery
16	48	Pseudo-obstruction	Duodenojejunostomy, ileorectal anastomosis	8	Multiple surgery
17	52	Crohn's disease	Short bowel, end ileostomy	1	Multiple surgery, recurrent pyelonephritis
18	61	Multiple abscesses and fistulae after emergency colectomy	End jejunostomy	4	Multiple surgery and abscesses
19	24	Visceral myopathy	Duodenojejunostomy, end ileostomy	3	Stomach does not empty
20	37	FAP with desmoids	End jejunostomy	4	Multiple surgery
21	41	Radiation enteritis	End jejunostomy	1	Para-aortic irradiation
22	33	Crohn's disease	End jejunostomy	3	Multiple surgery and fistulae
23	53	FAP with desmoids	Short bowel, end jejunostomy	1	Multiple surgery, difficult adhesions
24	27	Crohn's disease	Short bowel, jejunocolic anastomosis	3	Multiple surgery, abscesses, fistulae
25	47	Crohn's disease	Short bowel, end jejunostomy	3	Multiple surgery, fistulae, adhesions

FAP, familial adenomatous polyposis. *Multiple surgery represents more than three laparotomies

The suitability of each patient for transplantation was decided by the consultant concerned; there are no established criteria on which to base this decision. Early attempts at small bowel transplantation were carried out before the advent of parenteral nutrition in patients who could not have survived without a successful transplant²¹. More recently, small bowel transplantation has been used for patients already on parenteral nutrition but who have developed complications such as multiple venous thromboses restricting venous access²² or progressive liver failure²⁵⁻²⁷.

The aetiology of small intestinal failure in the patients who have received small bowel transplants was: volvulus (four patients)^{24,25,28,29}, congenital enteropathy (one)²⁷, necrotizing enterocolitis (one)²³, gastroschisis (one)²⁶, mesenteric band (one)³⁰, intussusception (one)³¹, trauma (three)^{22,23,32}, familial adenomatous polyposis with desmoids (three)³³⁻³⁵, thrombosis of the superior mesenteric artery (three)^{22,23,36} or vein (one)³⁷, and carcinoma (usually of the pancreas) (11)^{24,38}. In a further eight patients the aetiology was not reported. The appropriateness of transplantation for various categories of intestinal failure has been discussed elsewhere^{1,39,40}. In general, transplantation is considered inappropriate for patients with reversible intestinal failure and those with a very limited prognosis because of carcinoma or systemic disease. Within the group of patients with irreversible intestinal failure and an otherwise good prognosis, no consensus has been reached. The current study is the first attempt to define which individuals within a group of patients with intestinal failure might be candidates for transplantation.

In the future, the choice between parenteral nutrition and small bowel transplantation may resemble that today between dialysis and kidney transplantation for patients with renal failure. Refinements in immunosuppressive treatment should reduce the incidence of both rejection and graft versus host reactions, which have occurred in recent clinical transplants²³. Combined liver and small bowel transplantation appears less likely to provoke transplant rejection^{22,23} than isolated small bowel transplantation; the liver confers a degree of protection against rejection on other organs from the same donor⁴¹. Combined liver and small bowel transplantation is particularly appropriate for patients who develop liver failure as a result of long-term parenteral nutrition.

Approximately two adults per 1 000 000 per year start home parenteral nutrition in the UK² and it seems that half of these have irreversible small intestinal failure². This proportion is similar to that found in the USA⁴². However, in a series involving many European centres⁴³, only 37 of 108 patients continued home parenteral nutrition for over 1 year. Extrapolation of the North-East Thames Region results using UK population figures suggests that, if 12-40 per cent of those with irreversible small intestinal failure are suitable for transplantation, between six and 20 adult candidates annually in the UK might be treated by this method. We believe that, if a successful small bowel transplantation programme were established in this country, further patients would be put forward for both parenteral nutrition and transplantation. At present, it is often considered unreasonable to commit a patient to life-long parenteral nutrition; if transplantation became an available option, more hope for a reasonable future could be offered to those with irreversible small intestinal failure.

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Case report

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Perforation of the bowel by suction drains

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Surgical tradition dictates that a drain should be left in the peritoneal cavity as prophylaxis against fluid collection and subsequent abscess formation. 'If in doubt, drain' is a well known surgical maxim. Recently, open drains have been largely superseded by closed suction drainage systems. There have been few clinical studies of the effects of draining the abdominal cavity and those that have been undertaken have failed to demonstrate any benefit. Occasional reports of complications due to suction drains have appeared, and three cases are presented in which the use of suction drains resulted in perforation and peritonitis.

Patient 1

A 64-year-old man underwent splenectomy for traumatic rupture. A suction drain 2.5 mm in diameter was placed in the splenic bed. Five days later the patient developed peritonitis and a further laparotomy was performed. At operation a series of lesions was found in the fundus of the stomach relating to damage from the drain. A loop of small bowel was similarly affected (Figure 1). One of the lesions in the stomach had perforated, resulting in peritonitis. This was repaired and the patient made a satisfactory recovery.

Patient 2

A 25-year-old woman underwent right hemicolectomy for a bleeding arteriovenous malformation in the caecum. A suction drain 2.5 mm in diameter was left in the right paracolic gutter. This drained >100 ml/day and was left *in situ*. Six days after the operation the patient developed peritonitis. At laparotomy a series of lesions corresponding to the holes in the suction drain was found in a loop of small bowel distant from the anastomosis. One of these had perforated, resulting in peritonitis. The defect was repaired and the patient recovered to be discharged from hospital 4 weeks after admission.

Patient 3

A 75-year-old man underwent low anterior resection for a Dukes' B carcinoma of the rectum. A suction drain 5 mm in diameter was left



Figure 1 Small bowel injury caused by a suction drain

in the pelvis at the end of the procedure and removed 5 days later. Ten days after operation the patient developed abdominal distension and peritonitis. At laparotomy a series of lesions consistent with damage caused by the suction drain was found in a loop of small bowel in the pelvis. One of these lesions had perforated, resulting in a 3-mm defect. This was repaired and the patient made a satisfactory recovery.

Discussion

There have been two previous reports describing three cases of visceral injury caused by suction drains and resulting in postoperative peritonitis^{1,2}. Considering the widespread use of these drains this appears to be a rare complication, although it may have been under-reported. Laparotomy was required in each case reported here and recovery was protracted in one patient. In each, the drain was left in place for several days, which may have contributed to the resulting bowel injury.

Suction drains are frequently used after abdominal procedures despite the lack of evidence from controlled studies of any beneficial effect^{3,4}. On the evidence currently available there appears to be no basis for their continued use in the abdominal cavity. Suction drains may, in fact, be harmful.

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Flush aortic tie versus selective preservation of the ascending left colic artery in low anterior resection for rectal carcinoma

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The effects of two methods of colonic vascular ligation were studied in 143 consecutive patients who underwent low anterior resection with total mesorectal excision and full mobilization of the splenic flexure. Either the ascending left colic artery (ALCA) was selectively preserved (n = 52) or a flush aortic ligation was performed (n = 91). In those with a protective colostomy, the radiological leak rate was 12 per cent when the ALCA was preserved (n = 41) and 10 per cent when a flush aortic tie was performed (n = 60) (P > 0.05; 95 per cent confidence interval (c.i.) for difference -10 to +15 per cent). In those without a colostomy, the clinical leak rates of 9 per cent when the ALCA was preserved (n = 11) and 19 per cent when a flush aortic tie was performed (n = 31) were not significantly different (P > 0.10; 95 per cent c.i. for difference -12 to +32 per cent). Proportional hazards analysis showed no association between the method of vascular ligation and the risk of tumour recurrence and death. Anastomotic leak rates, tumour recurrence and survival were not related to the method of vascular ligation.

In this unit, colonic vascular ligation has been performed in one of two ways in patients undergoing low anterior resection with total mesorectal excision and full mobilization of the splenic flexure. Either the inferior mesenteric artery has been ligated flush with the aorta or the ascending left colic artery (ALCA) has been selectively preserved. Preservation of the ALCA may improve left colonic perfusion but makes the resection slightly less radical. The effect of this manoeuvre on anastomotic leak rate, tumour recurrence, and survival has been investigated.

Patients and methods

In a 10-year period, 143 patients with rectal carcinoma underwent low anterior resection with total mesorectal excision and full mobilization of the left colon and splenic flexure. The operations were all performed or personally supervised by one surgeon (R.J.H.). Operative and follow-up details were stored prospectively on a computer as described previously¹. The median distance of tumours from the anal verge at sigmoidoscopy was 7.0 (range 3.5-15) cm. All patients had a stapled end-to-end colorectal anastomosis at a median distance from the anal verge of 4.5 (range 1.0-8.0) cm.

The operations in these patients varied in only two respects. First, either the ALCA was selectively preserved (n = 52) or a flush aortic tie was performed (n = 91). Second, although a prophylactic defunctioning transverse loop colostomy was used in the majority (n = 101) of cases, this was discontinued for parts of the series because of reports questioning the need for this manoeuvre². Anastomotic leaks in those with a colostomy included all symptomatic leaks and also asymptomatic ones demonstrated by contrast enema performed in all patients before colostomy closure. In those without a colostomy, contrast enema was performed only when clinically indicated, so only symptomatic leaks were recorded in this group. Leak rates were therefore analysed separately in those with and without a prophylactic colostomy.

The ALCA was selectively preserved in 41 of 101 patients with a prophylactic colostomy; flush ligation was performed in the remainder. In 42 patients without a prophylactic colostomy, the ALCA was preserved in 11 and flush ligation performed in 31 (Table 1).

The technique of preservation of the ALCA is illustrated in Figure 1. This artery is present in approximately 75 per cent of cases and arises within 3 cm of the origin of the inferior mesenteric artery³. The ALCA runs up to the splenic flexure so that when the latter is mobilized it

may be brought down into the pelvis on a vascular pedicle. In association with separate high ligation and division of the inferior mesenteric vein (performed in all cases), this manoeuvre rarely produced vascular tethering. A flush tie (Figure 2) was used if there was nodal disease at the origin of the inferior mesenteric artery, or if the ALCA was absent or its preservation seemed likely to produce anastomotic tension. The method of colonic vascular ligation was not randomized. Patients in whom the ALCA was preserved were similar in age, sex and anastomotic height to those undergoing flush aortic ligation (Table 1).

The association between anastomotic leakage and colonic vascular ligation was analysed using the χ^2 test with Yates' correction. Proportional hazards analysis⁴ (program P2L; Biomedical Programs, UCLA, Berkeley, California, USA (1985)) was used to investigate the relationship between hazards of recurrence and death and the level of vascular ligation, Dukes' classification, distal clearance margin, age and sex. The results of the proportional hazards analysis are expressed as odds ratios, which approximate to relative risks.

Table 1 Comparison of anastomotic leak rate, anastomotic height and patient characteristics in patients who underwent anterior resection with preservation of the ascending left colic artery or flush ligation of the inferior mesenteric artery

	ALCA preservation	Flush ligation
With colostomy		
n	41	60
Leaks*	5 (12)	6 (10)
Median (range) anastomotic height (cm)	4.0 (2.0-6.0)	4.0 (1.0-8.0)
Median (range) age (years)	72 (38-90)	68 (39-88)
Without colostomy		
n	11	31
Leaks*	1 (9)	6 (19)
Median (range) anastomotic height (cm)	5.0 (2.5-8.0)	5.0 (3.0-8.0)
Median (range) age (years)	66 (27-83)	63 (41-86)

*Values in parentheses are percentages. ALCA, ascending left colic artery

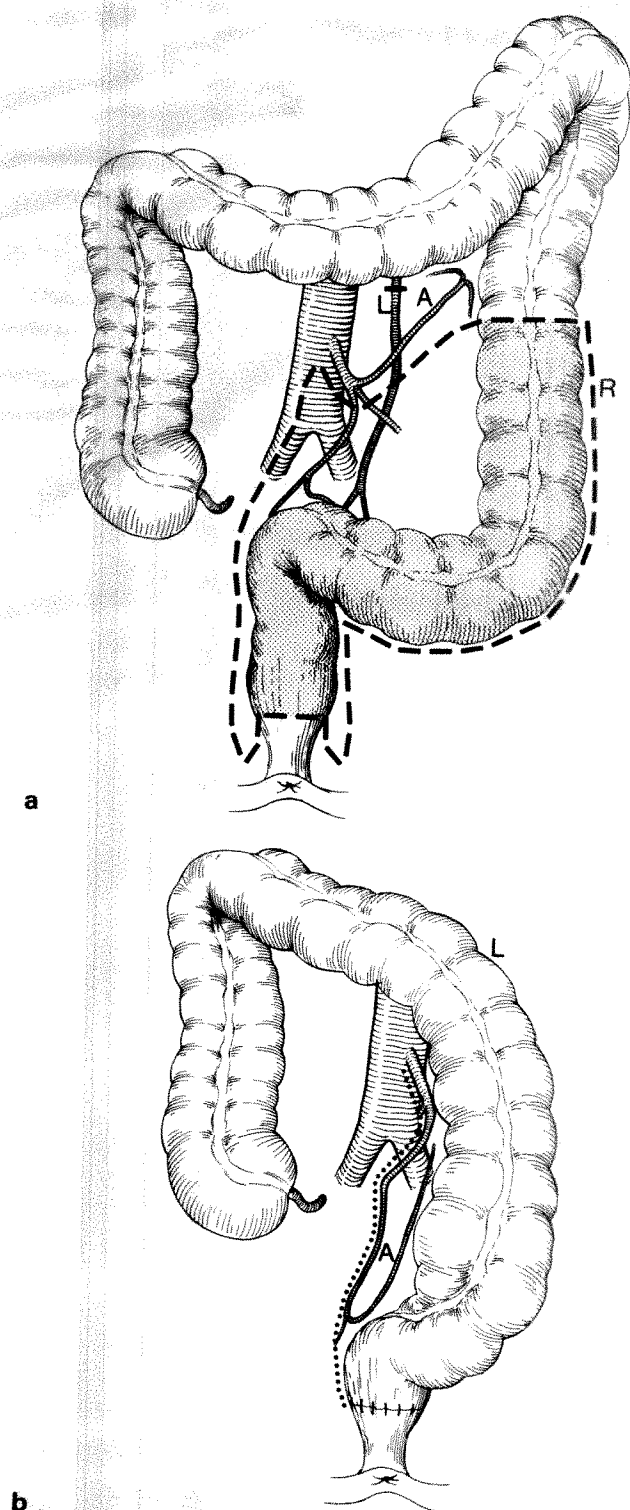


Figure 1 Colon and blood supply **a** before and **b** after low anterior resection with preservation of the ascending left colic artery. A, ascending left colic artery; L, site of ligation and division of the inferior mesenteric vein; R, extent of resection

Results

Radiological leakage in patients with a colostomy

Five of the 41 patients (12 per cent) in whom the ALCA was preserved developed leaks, compared with six of the 60 patients (10 per cent) having flush aortic ties ($P > 0.05$; 95 per cent confidence interval (c.i.) for difference -10 to +15 per cent).

Clinical leakage in patients without a colostomy

Leaks occurred in one (9 per cent) of the 11 patients in whom the ALCA was preserved compared with six (19 per cent) of

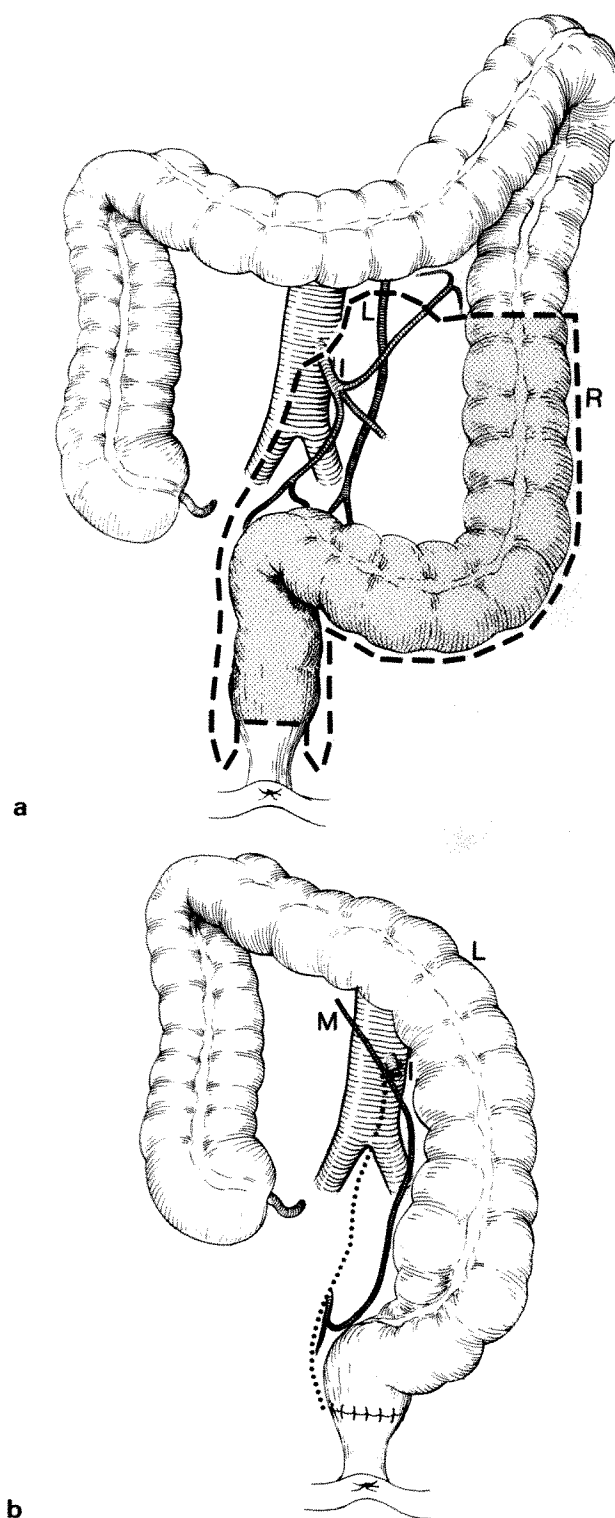


Figure 2 Colon and blood supply **a** before and **b** after low anterior resection with a conventional flush aortic tie. I, origin of the inferior mesenteric artery; L, site of ligation and division of the inferior mesenteric vein; R, extent of resection; M, marginal artery

the 31 with a flush aortic tie ($P > 0.10$; 95 per cent c.i. for difference -12 to +32 per cent).

Tumour recurrence and survival

Patients in whom the ALCA was preserved were followed up for a median of 35 (range 4-84) months. Those with flush aortic ties were followed up for a median of 82 (range 0-116) months. Proportional hazards analysis showed that the risk of tumour recurrence or death was not significantly influenced by the method of colonic vascular ligation. When this factor was

Table 2 Risks of tumour recurrence and death from any cause after anterior resection associated with preservation of the ascending left colic artery or flush ligation of the inferior mesenteric artery calculated using proportional hazards analysis (n = 143)

Risk factor	Relative risk of tumour recurrence	Relative risk of death
Preservation of ascending left colic artery versus flush aortic tie	1.1 (0.5-2.7)	0.9 (0.4-1.8)
Dukes' classification		
B versus A	4.3 (0.5-35)	4.5 (1.3-15)
C versus A	19 (2.6-149)	8.8 (2.5-31)
'D' versus A	—	65 (12-361)
Age (per year increase)	0.9 (0.4-1.9)	1.7 (0.9-3.1)
Distal clearance margin (per cm increase)	1.0 (0.97-1.02)	0.99 (0.98-1.01)
Sex (F versus M)	1.9 (0.9-4.0)	1.4 (0.8-2.4)

Values in parentheses are 95 per cent confidence intervals

analysed in isolation, the relative risk of tumour recurrence when the ALCA was preserved was 1.3 (95 per cent c.i. 0.6-2.8) and the relative risk of death 1.3 (95 per cent c.i. 0.7-2.4).

Similarly, when other factors were included in the analysis (Table 2), the method of colonic vascular ligation had no influence on the hazard of recurrence or death. The hazard of recurrence and death increased progressively with increasing Dukes' classification. Distal clearance margin, age and sex were not significantly related to the hazard of recurrence or death.

Discussion

An anastomosis free of tension with a good blood supply is of crucial importance in low anterior resection. Two ways in which this may be achieved have been examined in this paper. A flush aortic tie maximizes tumour clearance and colonic mobility, but leaves left colonic perfusion dependent on the marginal artery. Selective preservation of the ALCA may improve left colonic blood supply but may also inhibit left colonic mobility and render clearance of nodes slightly less radical. In all patients, high ligation and division of the inferior mesenteric vein was used to achieve maximal colonic mobilization. Although this study was not randomized, the two groups, within the subdivision of those with and those without a prophylactic colostomy, were closely similar in terms of age, sex and anastomotic height (Table 1). No association between the method of colonic vascular ligation and anastomotic leakage was shown. In the colostomy group at least, it is unlikely that this result is due to inadequate statistical power as shown by the narrow c.i. for the difference in leakage rates between those with and without ALCA preservation.

To the best of our knowledge, this is the only comparison of these two methods of colonic vascular ligation. Goligher *et al.*⁵ showed a slightly increased leak rate in patients undergoing low ligation of the inferior mesenteric artery, but this result was not statistically significant and anastomotic heights in the two groups were not presented. In our patients, both with and without a defunctioning transverse loop colostomy, anastomotic heights in those in whom the ALCA was preserved and those with flush aortic ties were similar.

Proportional hazards analysis showed no association between the method of colonic vascular ligation and the risk of tumour recurrence and death. This result was not changed when allowance was made for other variables and factors, including Dukes' classification. Proportional hazards analysis takes into account the different durations of follow-up in the two groups.

Patients with possible nodal disease at the origin of the inferior mesenteric artery were treated using flush aortic ligation. Our pathological staging did not distinguish between C₁ and C₂ disease. It is possible that the group treated by flush aortic ligation contained a disproportionate number of C₂ cases. A recent study has, however, shown no difference in survival between patient with Dukes' C rectal carcinoma having high or low ligation of the inferior mesenteric artery⁶. This result was not changed when allowance was made for stages C₁ and C₂.

The distal margin of clearance showed no association with the hazard of recurrence or death. This finding may be related to our practice of total mesorectal excision. It supports the view that much recurrence in the region of low rectal anastomoses arises in incompletely excised mesorectum⁷.

Selective preservation of the ALCA therefore produces no benefit in terms of decreased leak rate and no disadvantage in terms of recurrence and survival compared with a flush aortic tie. Although the two methods of vascular ligation involve identical amounts of colonic mobilization, selective preservation of the ALCA involves an additional step in vascular identification and dissection and is not applicable in all cases. Flush aortic ligation is therefore preferred as it is quicker, easier and more generally applicable.

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Mesosigmoidoplasty as a definitive operation for sigmoid volvulus

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In a prospective study, 126 patients with sigmoid volvulus were treated by mesosigmoidoplasty during a 12-year period. Patients with sigmoid volvulus with no clinical evidence of gangrene were selected for study, and all were given a trial of non-operative reduction by proctoscopy and passage of a rectal tube. Reduction was achieved in 48 patients (38 per cent), who were subsequently treated by mesosigmoidoplasty as an elective procedure 1-2 weeks later. For the remaining 78 patients (62 per cent) who were not relieved by the non-operative method, emergency mesosigmoidoplasty was performed. There was one death in the emergency group, and two patients had a recurrence after 2 and 6 months respectively in the elective group, in whom resection was carried out. In the other 123 patients during a maximum follow-up of 12 (mean 8.2) years no recurrence was detected. Mesosigmoidoplasty has the advantage of low rates of mortality, morbidity and recurrence; it can be carried out as either an emergency or an elective procedure.

Volvulus of the sigmoid colon, although uncommon in the west^{1,2}, is seen frequently in Africa, Iran, Russia and India³⁻⁶. It is a common surgical emergency and accounts for up to 30 per cent of all cases of intestinal obstruction occurring in India⁷.

Various approaches to the management of sigmoid volvulus have been reported, with varying results. Resection has been reported to be the best operative therapy^{2,6}. Other methods such as non-operative reduction with the colonoscope^{8,9}, sigmoidopexy^{7,10} and mesocoloplasty¹¹ have been suggested, but have been performed in only a few patients². In this communication, experience with mesocoloplasty - better called mesosigmoidoplasty - in the treatment of sigmoid volvulus over a 12-year period is described.

Patients and methods

A group of 126 patients with sigmoid volvulus treated at the general hospitals in Sangli and Solapur from January 1978 to December 1989 formed the basis of the study. Thirty-six patients with non-viable sigmoid colon who were treated during this period were excluded. The presenting symptoms and clinical features were noted. Plain radiography of the abdomen in the erect and supine positions was carried out. All patients were given a trial of conservative treatment by proctoscopy and passage of a rectal tube. Patients were divided into two groups for further treatment. In the elective group ($n = 48$), patients who were relieved by proctoscopy and rectal tube passage were treated by elective mesosigmoidoplasty after 1-2 weeks. In the emergency group ($n = 78$), patients unrelieved by proctoscopy and rectal tube passage were treated by emergency mesosigmoidoplasty.

Mesosigmoidoplasty was carried out under general anaesthesia. The abdomen was opened by a lower left paramedian incision. The distended sigmoid loop was delivered and untwisted. The viability of the loop was confirmed and the sigmoid colon deflated by passage of a rectal tube. The cause of the volvulus was ascertained. The length of the mesentery was measured from the base to the mesenteric border of the sigmoid colon; the base of the mesosigmoid was also measured. The peritoneum over the inner aspect of the mesosigmoid was incised vertically in the middle, starting from the base up to 2.5 cm from the mesenteric border of the sigmoid colon. The two flaps of peritoneum were raised laterally, taking care not to damage the underlying vessels. These flaps were united transversely by continuous suturing using chromic catgut. The procedure was repeated with the peritoneum over the outer aspect of the mesosigmoid. The mesosigmoid was thus shortened by bringing the loop closer to its base and broadening it (Figures 1-3). After completion of the procedure, the length of the mesosigmoid and its base were measured. The abdomen was closed in

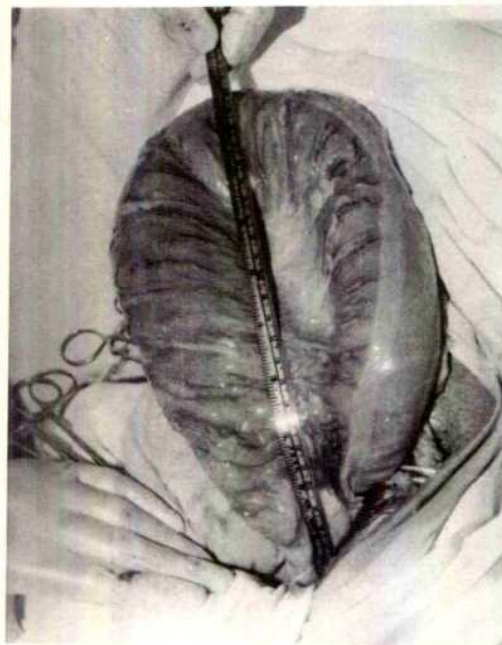


Figure 1 Sigmoid colon showing long mesosigmoid and narrow attachment at the base

layers and management thereafter was similar in all cases. Patients were followed up for evidence of complications or recurrence.

Results

There were 84 men and 42 women, with an age range of 32-68 years. The majority were aged 51-60 years (Table 1). Ninety-two patients belonged to the low income group and most were agricultural labourers. All were used to a mixed diet.

Abdominal distension (85 per cent), constipation (85 per cent), and nausea and vomiting (22 per cent) were the main symptoms. The mean interval between onset of symptoms and admission was 48 h. Eighteen patients had had previous episodes with spontaneous reduction and none had undergone any previous abdominal operation or suffered from any psychiatric illness. Plain abdominal radiography showed the classical 'bent inner tube sign' in 98 per cent of cases. After treatment with proctoscopy and passage of a rectal tube, 48 patients had reduction, and elective mesosigmoidoplasty was

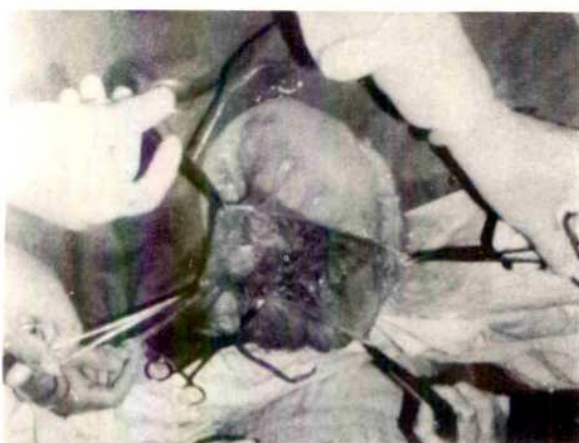


Figure 2 Flaps of the peritoneum being raised laterally after making a vertical incision

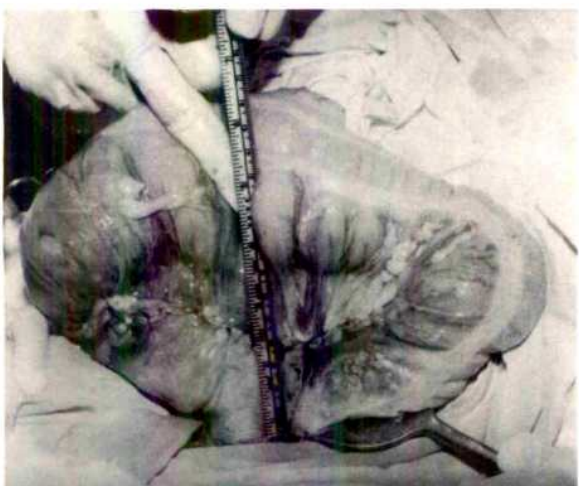


Figure 3 Loop after mesosigmoplasty showing reduction in length and broadened base

performed after 1–2 weeks; 78 patients who did not obtain relief by this method underwent emergency mesosigmoplasty. At operation all had a viable and distended sigmoid with volvulus of the mesenteric base. None had megacolon, melanosis coli, or a loaded sigmoid. In one patient there were adhesions which were separated. Measurement revealed a long mesosigmoid in all patients; the base was narrow. After mesosigmoplasty the length of the mesosigmoid was reduced and the base broadened significantly ($P < 0.001$, Student's paired t test) (Table 2).

The mean operation time was 38.8 min. There was no difficulty in raising the peritoneal flaps laterally and suturing them transversely, no damage to the vessels underneath, and no congestion of the sigmoid in any patient. There was one death in the emergency group. This patient had carcinoma of the larynx which was detected by the anaesthetist while removing the endotracheal tube after operation. The patient died 2 days later from aspiration pneumonia. Wound infection occurred in two cases in the emergency group and this responded to routine treatment. Two patients in the elective group had a recurrence of sigmoid volvulus at 2 and 6 months respectively after operation. They underwent a sigmoid resection and subsequently did well. Of the remaining 123 patients, 39 were followed up for 2–6 years, 46 for 6–8 years, 20 for 8–9.5 years, 12 for 9.6–11 years and six patients for 11–12 years (overall mean 8.2 years). During follow-up none was found to have a recurrence.

Discussion

The common causes of sigmoid volvulus are long mesentery with narrow attachment, loaded loop, pregnancy, congenital

Table 1 Age and sex of 126 patients treated by mesosigmoplasty

Age group (years)	Elective group		Emergency group	
	M	F	M	F
30–40	2	0	0	1
41–50	11	2	12	7
51–60	14	9	29	14
61–70	7	3	9	6
Total	34	14	50	28

Table 2 Mesosigmoid length and base in 126 patients before and after mesosigmoplasty

	Before mesosigmoplasty	After mesosigmoplasty
Length of mesosigmoid (cm)	24.2(0.2)	16.2(0.2)
Base of mesosigmoid (cm)	6.4(0.5)	12.3(0.1)

Values are mean(s.d.). $P < 0.001$ (Student's paired t test)

malformation, and chronic constipation. A high-fibre diet has also been blamed for the high incidence of this condition in India, Africa and Iran^{6,7}. Of all these factors, long length and narrow attachment of the mesentery have been found in many affected patients at operation^{6,7,12}.

Various operative procedures have been tried for sigmoid volvulus and the recommended therapy for this condition is generally resection. Operative derotation without further treatment leads to recurrence^{2,6}. Similarly, non-operative reduction with the colonoscope has given good results, but recurrence is common^{8,9}.

In this study mesosigmoplasty has been tried as a definitive operative treatment for sigmoid volvulus. It reduces the length of the mesosigmoid and broadens its attachment, which are the important aetiological factors in the condition. There were only two cases of recurrence at 2 and 6 months respectively after operation and these were easily treated by resection. Mesosigmoplasty has a low rate of operative mortality and morbidity. It is easy to perform and can be carried out as an elective or emergency procedure; no bowel preparation is required.

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Primary versus staged resection for acute obstructing colorectal carcinoma

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The management of 115 patients with complete neoplastic obstruction of the colon was studied retrospectively. Primary resection was carried out in 40 patients, 22 with right-sided and 18 with left-sided tumours. Staged resection was planned in 48 patients and actually performed in 40. Creation of a stoma only was carried out in 25 patients because of advanced disease. There were no differences between primary and staged resection regarding the patients' general condition, concurrent disease, tumour stage according to Dukes' classification, postoperative complications, or mortality. The postoperative mortality rate was 10 per cent after primary and 15 per cent after staged resection (P not significant). The median hospital stay was 18 and 45 days, respectively. The 5-year survival rate was 38 per cent after primary and 29 per cent after staged resection. All primary resections but one were performed by qualified surgeons, while trainees created stomas as emergency treatment. The similarity in outcome suggests that in future this condition should, where possible, be treated by primary resection, by surgeons experienced in colorectal operations.

The surgical approach to obstructing carcinoma of the colon has been controversial for many years. According to traditional teaching the first objective is to decompress the intestine by proximal enterostomy, postponing resection of the tumour to a second operation¹⁻⁵. Surgeons have preferred to resect right-sided tumours, probably because the alternatives of ileostomy, caecostomy or bypass ileocolostomy are less attractive in comparison with the simpler resection of a tumour of the ascending colon^{2,6,7}. From a practical viewpoint, the conflict therefore concerns the treatment for tumours of the transverse or descending and sigmoid colon⁸⁻¹². As the alternatives of primary resection and traditional staged resection have not been the subject of a prospective randomized trial, and perhaps never will be, conclusions regarding these two methods must be drawn through retrospective analysis. The clinical problem is often difficult because not only must characteristics of the tumour be considered, but also the general condition of the patient and the experience of the surgeon. A retrospective analysis is reported of 115 patients with completely obstructing carcinoma from an area serving a population of 300 000. Factors relating to the tumour, the patient, and clinical management were studied to evaluate their influence on the decision to perform primary or secondary resection, and on the outcome of each procedure.

Patients and methods

The records of patients with acute obstructing colorectal cancer during 1971-1986 in three hospitals were reviewed. Those with complete obstruction as verified by barium enema were included, but patients were excluded if the contrast medium passed the stenotic tumour. A total of 115 patients who had been operated on met these criteria.

The median age was 73 (range 43-90) years. The general condition of the patient on admission was assessed by bedside examination and laboratory tests. Details were recorded of abdominal pain, fluid and electrolyte balance, circulatory state and respiratory function. The patient's general condition was classified as good or fair if homoeostasis, circulation and respiration were near normal, equivalent to an acute physiology score (APS)¹³ ≤ 2 , but was rated as poor with higher APS values. Concurrent disease was recorded as insulin-treated diabetes mellitus, chronic respiratory or cardiovascular disease, chronic renal failure, or dementia. In most instances the chronic disease had been ameliorated with appropriate medication.

The duration of acute symptoms was grouped as 1-3, 4-7 or >7 days. The operation start time was recorded as daytime (07.00-17.00 hours), evening (17.00-23.00 hours), and night-time (23.00-07.00 hours). The surgeon was recorded as trainee (experience <5 years) or qualified. Potentially resectable tumours were those that it was planned to resect at a second operation. Irresectable tumours were those that had been examined *in situ* but had been found to be impossible to remove. Resected tumours were staged according to Dukes' classification¹⁴.

Postoperative complications were recorded in surviving patients as wound infection (pus in wound), pneumonia (radiographic confirmation), urinary tract infection (culture $\geq 10^5$ organisms per ml) or unexplained fever (temperature $\geq 38.5^\circ\text{C}$ for >2 days). Non-infective complications were anastomotic leak or fistula, or thromboembolism verified by plethysmography or pulmonary scintigraphy. Hospital mortality was defined as death from any cause during hospitalization for the colonic obstruction. The length of stay, morbidity and mortality for reconstruction of bowel continuity after Hartmann's procedure or simple closure of a protecting stoma were included in the data. The crude survival rate after resection was based on the intention to treat ($n = 88$) and calculated as the percentage of patients remaining alive after 2 and 5 years.

Statistical comparisons were carried out using Fisher's test.

Results

Tumour location and Dukes' classification

The tumours were located as shown in Table 1; those proximal to the splenic flexure were considered to be right-sided (37 per cent) and all others as left-sided (63 per cent). Dukes' classification showed no significant difference between right- or left-sided tumours or between patients treated by primary or staged resection (Table 2). Only 4 per cent of the carcinomas were restricted to the muscularis propria (Dukes' A) while 15 per cent had distant metastasis. An additional 39 per cent had lymphatic invasion.

Preoperative findings

The duration of symptoms of colonic obstruction was short (1-3 days) in 54 per cent of patients, 4-7 days in 21 per cent and >7 days in 25 per cent. Concurrent disease was present in almost half of the patients. The general condition on admission of those who underwent primary resection was good

Table 1 Distribution and management of malignant tumours causing complete obstruction of the colon and rectum

Location	Total (n = 115)	Primary resection (n = 40)	Decompressive stoma		
			Potentially resectable (n = 48)	Irresectable* (n = 25)	Exploratory laparotomy (n = 2)
Caecum, ascending colon, hepatic flexure	25	13	3 (1)	9	0
Transverse colon	18	9	5 (2)	4	0
Splenic flexure, descending colon	16	5	9 (9)	2	0
Sigmoid colon	50	13	27 (26)	8	2
Rectum	6	0	4 (2)	2	0

Values in parentheses are numbers undergoing staged resection. *Primary resection was planned in six patients

Table 2 Dukes' classification related to location and primary or staged resection

	Dukes' classification			
	A	B	C	'D'
Location				
Right colon (n = 25)	0	12	9	4
Left colon (n = 55)	3	22	22	8
Resection				
Primary (n = 40)	1	19	13	7
Staged (n = 40)	2	15	18	5

Table 3 Preoperative findings and time of surgery in 40 patients undergoing primary resection of an obstructing colonic cancer

	Right colon (n = 22)	Left colon (n = 18)
General condition		
Good or fair	20	15
Poor	2	3
Concurrent disease	11	7
Time of surgery		
07.00–17.00 hours	8	4
17.00–23.00 hours	7	10
23.00–07.00 hours	7	4

or fair in 35 patients (88 per cent) and poor in five (12 per cent). The corresponding figures for patients with resectable carcinoma treated initially by formation of a stoma were 40 (83 per cent) and eight (17 per cent), not significantly different. The preoperative condition, presence of concurrent disease, and time of the day for surgery did not vary with the site of the tumour in patients treated by primary resection (Table 3). Nor did preoperative findings or time for surgery differ in those with left-sided tumours who underwent primary resection or had a staged procedure (Table 4). The median ages of patients undergoing primary and staged resection were 75 and 73 years, respectively, which is not significant for selection.

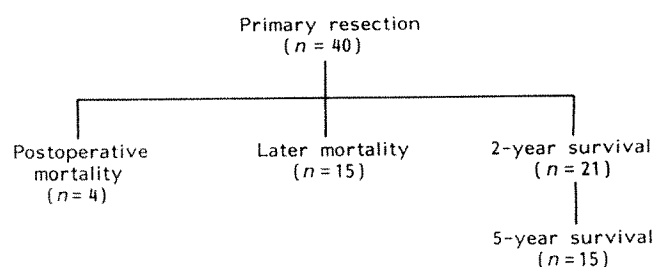
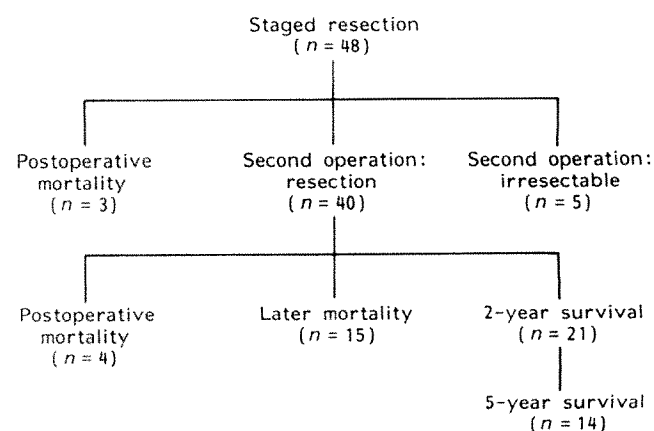
Surgical treatment

The first operation was primary resection (n = 40), staged resection (n = 48), stoma formation only (n = 25) or exploratory laparotomy (n = 2). Primary resection was performed in 22 of 30 (73 per cent) patients with right-sided tumours but in only 18 of 58 (31 per cent) with left-sided tumours. With a single exception, primary resection was chosen only by the qualified surgeon, while trainees always relied on a staged resection.

Among the 40 patients undergoing primary resection (Figure 1), 29 had an anastomosis fashioned, two of which were protected by a stoma. In the other 11 patients resection was performed as a Hartmann procedure. Figure 2 shows the course

Table 4 Preoperative findings in 55 patients with resectable tumours located in the left colon

	Primary resection (n = 18)	Stoma formation (n = 37)
General condition		
Good or fair	15	31
Poor	3	6
Concurrent disease	7	12

**Figure 1** Outcome in 40 patients with complete neoplastic large bowel obstruction treated by primary resection**Figure 2** Outcome in 48 patients with complete neoplastic large bowel obstruction treated by staged resection

of the 48 patients in the staged resection group. Only 40 of these patients underwent secondary resection, all by qualified surgeons. Five patients had an irresectable tumour at the second laparotomy, while three died after stoma formation.

Postoperative mortality

The overall postoperative mortality rate was 19 of 115 (17 per cent) (Table 5). The median age of patients who died was 76 years. The causes of death were heart failure (n = 12), bronchopneumonia (n = 3), thromboembolism (n = 1) and

Table 5 Causes of postoperative mortality in 115 patients with complete obstruction from colorectal carcinoma

Cause	Staged resection			Irresectable	
	Primary resection (n = 40)	Resection (n = 40)	Stoma formation (n = 48)	Stoma formation only (n = 25)	Exploratory laparotomy (n = 2)
Heart failure	3	3	2	4	0
Bronchopneumonia	0	0	1	2	0
Thromboembolism	0	0	0	0	1
Multiple organ failure	1	1	0	0	1
Total	4 (10)	4 (10)	3 (6)	6 (24)	2 (100)

Values in parentheses are percentages

multiple organ failure ($n = 3$). Among patients who underwent resection, four died after both primary and secondary resection (10 per cent for each procedure). Another three patients died after the initial stoma operation of a planned staged resection.

The mortality rate in patients undergoing primary resection for tumours of the right side was three of 22 (14 per cent) and of the left side one of 18 (6 per cent). This difference was not statistically significant.

Postoperative complications

Infective complications occurred in two patients after primary resection and in seven after staged resection, five of these after initial stoma formation. Two patients had thromboembolism after initial stoma formation, and miscellaneous complications (anastomotic leak, enterocutaneous fistula, subcutaneous wound dehiscence, stenosis of stoma, haematemesis) were seen in four patients after primary resection and in one after stoma formation and staged resection. Thus, postoperative complications were seen in 15 per cent of patients after primary resection and in 25 per cent after staged resection (5 per cent after bowel resection). Among patients undergoing primary resection, complications occurred in 14 and 17 per cent of those with right- and left-sided tumours, respectively. The complication rate after secondary resection of left-sided tumours was 5 per cent, again less than when such tumours were resected at the primary operation. None of these differences was statistically significant.

Hospital stay

After primary and staged resection the median hospital stay was 18 and 45 days, respectively. For left-sided tumours only it was 19 days after primary resection and 41 days after staged resection.

Survival

The 2-year crude survival rate was 52 per cent (21 of 40) in the primary resection group and 44 per cent (21 of 48) in the staged resection group (21 of 40 (52 per cent) in those who completed treatment). The 5-year survival rate was 38 and 29 per cent (35 per cent after completed staged resection), respectively (P not significant).

Discussion

Carcinoma of the colon and rectum can ultimately result in a circular stenosis of the bowel. If the obstruction is complete a well defined emergency situation arises. Such a carcinoma is obviously an advanced disease carrying a worse prognosis than one without obstruction^{15,16}. Only 4 per cent of the tumours in this study were Dukes' A, but more than half were Dukes' C or 'D'. The incidence of carcinomatous obstruction of the colon ranges from 10 to 30 per cent but is much influenced by the definition of this condition¹⁶⁻²¹. If tumours with some passage of contrast medium are included, the definition becomes more arbitrary. The present study considered only cases of complete obstruction as shown by barium enema, and patients

with perforation in addition to complete obstruction were not included.

Eighty-eight patients were considered as having potentially resectable tumours but only 40 underwent primary resection. Right-sided tumours were more often resected, but otherwise no important differences could be demonstrated for those treated by primary resection and those undergoing decompressive enterostomy. Patient-related variables such as general condition, concurrent disease, duration of symptoms, or tumour stage were the same as reported elsewhere⁴ and there were no differences between the groups of patients; nor was daytime *versus* night-time surgery a determinant of procedure. The only difference involved a manpower-related factor: in one in three cases, decompressive stoma formation was carried out by trainee surgeons while qualified surgeons performed all primary resections (except for one case). The reason for this difference cannot be determined retrospectively, as it relates to the management of individual patients and reflects the prevailing concepts and organization during the period. More advanced trainee surgeons were entrusted with the formation of a stoma while qualified surgeons, especially those trained in coloproctology, were inclined to resect the tumour. This shows that to favour primary resection it is necessary to change procedures.

Two concerns about resection and primary anastomosis are the risk of infection and anastomotic dehiscence. Both complications were uncommon after primary resection for both right- and left-sided tumours.

Complications after decompressive enterostomy were comparable to those after primary resection. A contributing factor to the rate of septic complications after construction of a simple stoma may be that the underlying disease was not removed and the stoma leaves a column of faeces impacted proximally to the tumour. Others have recently reported a morbidity rate of 37 per cent resulting from colostomy itself⁴. On-table lavage as described by Dudley *et al.*²² was performed in too few of the present cases to allow an evaluation.

Complete obstruction from cancer of the large bowel has a substantial mortality rate of 10-20 per cent^{9-11,14,23-25}, rising as high as 38 per cent⁵. In the present study 10 per cent of patients died after primary resection (four of 40) and 15 per cent after staged resection (seven of 48). Those who died were elderly (median age 76 years), and most had cardiac failure. A staged resection apparently does not carry the patient safely over the emergency. Stoma formation carried a considerable morbidity rate, while the postoperative mortality rate was not increased by resection, in agreement with results from other studies^{15,18,26}. The 5-year survival rate was the same for primary and staged resection. This agrees well with some reports^{7,23}, although others have found an improved survival rate among patients undergoing primary resection^{21,24}.

The major results of the present study are that while patient-related factors and outcome did not differ between those undergoing primary or staged resection, the choice between the two procedures was greatly influenced by the experience of the surgeon. Sufficient evidence now exists to support new

guidelines for the clinical management of patients with obstructing colorectal cancer. There should be three aims: primary resection, by a colorectal surgeon, during the daytime.

It is important to allow sufficient time for the evaluation and preparation of the patient, most of whom are elderly with concurrent disease and obstruction that has lasted for several days. Patients have not been eating, drinking, or attending adequately to their regular medication during their illness. The resulting physiological derangement must be carefully studied and corrected. This may require preparation in the intensive care unit to ensure optimum support of all body systems. Only when this has been accomplished is the patient ready for surgery.

The operation must expose the tumour for evaluation of its spread and resectability. Clinical judgement as to which operation is preferred for the patient will often be difficult; the trained colorectal surgeon is best placed to choose between the available alternatives. Extended resection with ileocolic anastomosis is probably to be preferred over on-table lavage. The risk of contamination is diminished if a competent ileocaecal valve has prevented flux of colonic contents into the ileum, allowing normal small bowel to be anastomosed to clean colon distal to the tumour. The rectosigmoid tumour is the major problem. In most instances resection with colocolic anastomosis is possible, but occasionally resection with closure of the rectum is a suitable alternative. It is usually not necessary to operate on the patient during the night. These difficult patients benefit more from the combined expertise available in the daytime in most hospitals.

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Role of congenital hypertrophy of the retinal pigment epithelium in the predictive diagnosis of familial adenomatous polyposis

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A study was carried out to evaluate congenital hypertrophy of the retinal pigment epithelium (CHRPE) as a disease marker in a defined population with familial adenomatous polyposis (FAP). Indirect ophthalmoscopy was performed on 75 individuals from 25 known families with FAP, of whom 32 were known to be affected and 43 were at a 50 per cent prior risk of developing the disease. A further ten individuals from five families with hereditary non-polyposis colorectal cancer (HNPCC) were also tested. CHRPE was seen in 28 of the 32 affected individuals, 27 of whom met the criteria for a positive examination. Three individuals at risk of FAP also had positive examinations. Five individuals from the families with HNPCC also had CHRPE, although none met the criteria for a positive examination. Of four types of CHRPE analysed, one (small pigmented dots) was found to be more frequent in older family members ($P = 0.012$), suggesting that this type of lesion may proliferate with age. Compliance with ophthalmic screening was 97 per cent in families with FAP. Using a combined set of diagnostic criteria, CHRPE identified affected individuals with a specificity of at least 94 per cent and a sensitivity of 84 per cent. Results argue for a combined screening programme for FAP of DNA analysis, indirect ophthalmoscopy and bowel examination.

Familial adenomatous polyposis (FAP) is a condition, inherited in an autosomal dominant fashion, that predisposes affected family members to the development of colorectal cancer. Although FAP is rare, with an estimated incidence of about one per 10 000 live births¹⁻³, it is an important, preventable cause of colorectal carcinoma. The pathognomonic feature of the disease is the development of hundreds, if not thousands, of adenomatous polyps throughout the large bowel. These do not usually appear until the second decade of life and may not be apparent until the fourth^{2,4}. Left untreated, they progress inevitably to colorectal carcinoma, usually in the fourth decade¹. The polyps always precede the development of colorectal carcinoma and have therefore been widely used as markers of the disease in affected families for over 50 years⁵. Unfortunately, because the age of onset of polyps is variable, to exclude the presence of FAP, bowel screening must be continued until at least 40 years of age. As a consequence, other diagnostic measures, which may have greater predictive value, have been investigated. One such test is indirect ophthalmoscopy, which can be used to identify the presence or absence of areas of congenital hypertrophy of the retinal pigment epithelium (CHRPE).

Abnormalities of the retina were first described⁶ in association with FAP in 1935, but it was not until 1980 that the potential for CHRPE as a marker of the disease was recognized⁷. Initially it was believed that CHRPE was associated only with Gardner's syndrome⁸. Subsequent studies from the USA⁹, Japan¹⁰ and the UK¹¹ have shown CHRPE to be present in a high proportion of FAP family members (65-100 per cent) with and without the extracolonic features of Gardner's syndrome. In fact, this syndrome is no longer regarded as clinically distinct from FAP, and CHRPE has been found to be equally prevalent in both forms of the condition^{12,13}.

In this population-based study the ophthalmic findings from 25 families in the West Midlands with FAP were analysed to

identify criteria for incorporating CHRPE into an integrated screening programme for the disease¹⁴.

Patients and methods

Study design

In 1988 a regional register of families with FAP was established in the West Midlands. Forty-seven families were notified to the register before July 1990. A diagnosis of FAP was confirmed from histology reports and in six cases by review of the sections and colectomy specimens of affected family members. Complete family pedigrees were constructed by regional genetics nurses. All affected family members and all those at 50 per cent prior risk (by birth) were invited to attend a genetics clinic for counselling. Clinical details were recorded at the same visit and checked with available medical records. In cases at risk for whom recent bowel examination had not been performed, an appointment was made. Since March 1990, a combined genetics and ophthalmology clinic has been established at East Birmingham Hospital (C.M.M., J.G.). Patients living in the north of the region were invited to attend North Staffordshire Royal Infirmary for ophthalmic examination (R.B.).

Patients

Seventy-seven individuals from 26 different families with FAP were invited to attend for indirect ophthalmoscopy and genetic counselling before December 1990. Two individuals from one family declined the invitation; there remained 75 individuals from 25 families for inclusion in the study. The family members studied were either known already to be affected, or born with a 50 per cent risk of developing the condition but had no colorectal polyps at their last bowel examination. A further ten individuals from five families with hereditary non-polyposis colorectal cancer (HNPCC) were also examined. These included three families with an autosomal dominant mode of inheritance. Of these, one pedigree fitted a Lynch type II and two a Lynch type I pattern of inheritance¹⁵. In the remaining two families the mode of inheritance was uncertain. The details of the study groups are shown in Table 1.

Indirect ophthalmoscopy

All individuals were examined after full pupillary dilatation using

Table 1 Details of 75 individuals from 25 families with familial adenomatous polyposis and ten from five families with hereditary non-polyposis colorectal cancer who underwent ophthalmic examination

Status of individuals	No. of individuals			Mean age (years)	No. of families
	M	F	Total		
Familial adenomatous polyposis					
Affected	17	15	32	35 (13–63)	20*
At 50% prior risk	18	25	43	26 (8–63)	16*
Hereditary non-polyposis colorectal cancer	7	3	10	41 (14–68)	5
Total	42	43	85	31 (8–68)	30

Values in parentheses are ranges. *Eleven families contained both at-risk and affected individuals

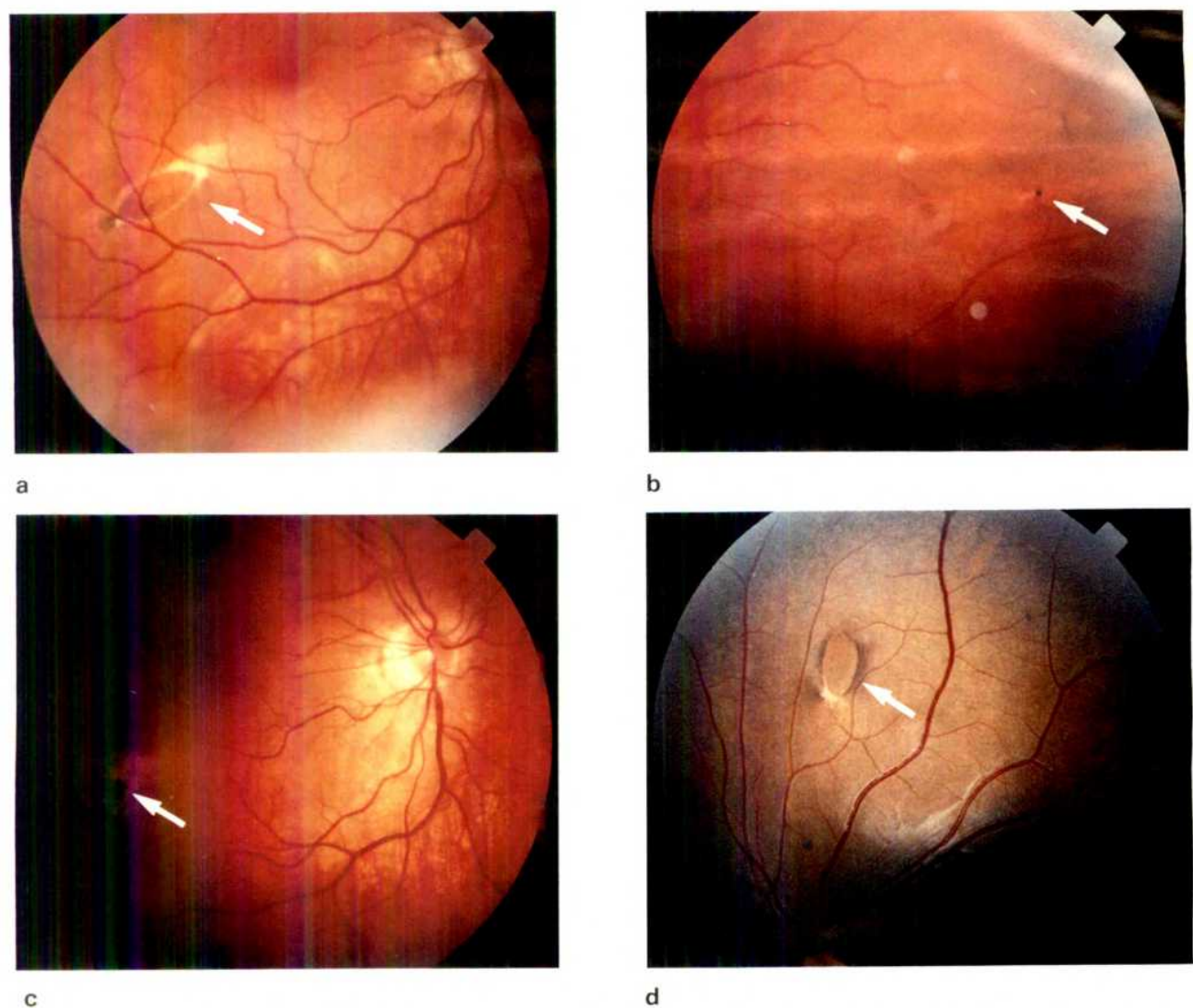


Figure 1 Four types of congenital hypertrophy of the retinal pigment epithelium. **a** Oval pigmented with halo; **b** small round pigmented dots; **c** large round pigmented dots; and **d** large round depigmented dots

1 per cent tropicamide and 2.5 per cent phenylephrine. Both eyes were examined with binocular indirect ophthalmoscopy using a 20-D lens and also a 90-D lens with slit-lamp biomicroscopy. The examination was carried out by one of two consultant ophthalmologists (J.G., R.B.), both of whom were unaware of the disease status of each patient. At each examination the number, size, position and type of lesions were noted. Findings were documented on retinal charts and photographic records kept when possible. CHRPE was subclassified by appearance into four different types of lesion, as described by Berk *et al.*¹⁶. These are: type a, oval pigmented with halo (Figure 1a); type b, small round pigmented dots (Figure 1b); type c, large round pigmented dots (Figure 1c); and type d, large round depigmented dots (Figure 1d).

The cases of CHRPE found in FAP family members were

subclassified into three age groups: 8–19, 20–34 and ≥ 35 years. The frequency of each type of lesion was calculated in each group.

Interpretation of findings

Based on the findings from previous studies^{9,11,12,16}, a positive ophthalmic examination was defined as fulfilling two of the following three criteria: (1) the presence of bilateral lesions; (2) the presence of three or more lesions; and (3) the presence of any lesion >0.3 optic discs in diameter.

Statistical analysis

Multiple analysis between groups was undertaken using the Kruskal–Wallis test. Where significance was attained ($P < 0.05$), subsequent analysis was undertaken using the two-tailed Mann–Whitney *U* test.

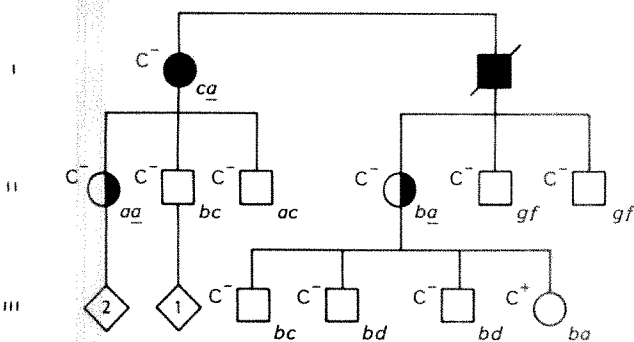
Table 2 Results from 85 ophthalmic examinations of 75 individuals from families with familial adenomatous polyposis and ten from families with hereditary non-polyposis colorectal cancer

Status of individuals	No. of individuals	CHRPE examination	
		Positive	Negative
Familial adenomatous polyposis			
Affected	32	27	5 (1)
At 50% prior risk	43	3	40 (1)
Hereditary non-polyposis colorectal cancer	10	0	10 (5)
Total	85	30	55 (7)

Values in parentheses are numbers of individuals with congenital hypertrophy of the retinal pigment epithelium (CHRPE) who did not meet the diagnostic criteria and are included in the total number of negative examinations

Table 3 Number of cases with each of the diagnostic criteria of congenital hypertrophy of the retinal pigment epithelium from 30 individuals with positive examinations

Nature of lesion	No. of cases
Bilateral	26
Three or more	23
Any >0.3 optic discs in diameter	20

**Figure 2** A pedigree with incomplete penetrance of the congenital hypertrophy of the retinal pigment epithelium (CHRPE) phenotype. No CHRPE was seen in the three affected family members, but CHRPE was present in a young daughter (III.7), who was also shown to be carrying the high-risk haplotype (a) using linked polymorphic DNA probe analysis. □, Male; ○, female; ■, deceased; ◇, unscreened; ●, colonic polyposis; ●, polyposis plus colorectal cancer; C+, multiple CHRPE present; C-, no CHRPE seen; a, high-risk haplotype; a, b, c, d, f, g, low-risk haplotype

Results

CHRPE was seen in 32 individuals from families with FAP, of whom 28 were known to be affected gene carriers at the time of investigation. Of these cases, 30 fulfilled the diagnostic criteria for a positive examination, 27 of whom were known to be affected (Table 2). Five patients with HNPCC had CHRPE, but none fulfilled the diagnostic criteria. Findings from the 30 positive examinations are shown in Table 3.

Five of the 32 affected individuals did not have positive examinations. These cases came from four of the 20 families. At least one pedigree with incomplete penetrance for the CHRPE phenotype was identified (Figure 2). In this case the daughter, who is as yet unaffected, had multiple CHRPE but none of the affected relatives, including the affected mother, had CHRPE. There were only three positive examinations in the at-risk group. However, in one sense this group was preselected, because the majority of affected individuals would already have manifested the disease. Indeed, as the at-risk group becomes older it can be considered to be an unaffected control group¹⁴. The mean age of the 43 individuals in the group at 50 per cent prior risk was 26 years at the time of examination, so 90 per cent of gene carriers would have been expected to have manifested the disease before examination⁴. The three positive findings in this group represent potential predictive diagnoses; all three patients were aged ≤18 years. One manifested the disease 1 year after ophthalmic examination, another has had a solitary colonic adenomatous polyp resected endoscopically, and the third has been shown using polymorphic DNA probes to be carrying the high-risk allele (Figure 2). Therefore, in all three cases there is corroborative evidence to suggest a diagnosis of FAP.

All four types of lesion were identified in the study population (Table 4). There was no difference in the distribution of lesions between the sexes, or between left and right eyes. The mean number of lesions in each age band was 3.9 (age 8–19 years), 7.5 (age 20–34 years), and 6.7 (age ≥35 years). Although an increase in the total number of lesions was demonstrated in the older age bands, this was not statistically significant. Subclassifying CHRPE into the four types of lesion showed that the increase was largely limited to those of type b, for which the rise in number was statistically significant ($P = 0.04$, Kruskal–Wallis test; $P = 0.012$, Mann–Whitney U test) (Table 4). No significant differences with respect to age were found with either type a or c lesions. There was an increase in the number of type d lesions with age, but this also was not statistically significant, possibly because of the small number of lesions involved.

Discussion

CHRPE has been found in babies from families with FAP as young as 3 months of age, and its presence before the development of colonic polyps has been established⁹. This study suggests that type b lesions may proliferate with age;

Table 4 Distribution of types of congenital hypertrophy of the retinal pigment epithelium according to age

Age (years)	No. of individuals	No. of lesions according to type*				Total no. of lesions
		a	b	c	d	
8–19	8	5 (4) [0.5 (0–2)]	12 (4) [1 (0–4)]	12 (7) [1 (0–5)]	2 (2) [0 (0–1)]	31
20–34	11	5 (5) [0 (0–1)]	49 (11) [5 (2–8)]	19 (9) [2 (0–4)]	9 (5) [0 (0–3)]	82
35–56	13	6 (6) [0 (0–1)]	57 (12) [3 (0–10)]	15 (6) [0 (0–5)]	9 (6) [0 (0–3)]	87
Total	32	16	118	46	20	200

Values in parentheses are numbers of patients with each type of lesion. Values in square brackets are median (range) numbers of lesions. *a, Oval pigmented with halo; b, small pigmented; c, large pigmented; d, large depigmented

Table 5 Findings from six studies of congenital hypertrophy of the retinal pigment epithelium in known affected individuals with and without familial adenomatous polyposis

Study	No. of families	No. of cases	Percentage of cases with CHRPE			
			With FAP		Without FAP	
			Total	Bilateral	Total	Bilateral
Traboulsi <i>et al.</i> ⁹ Baltimore, Maryland, USA	16	41	90	78	33 (42)	5
Berk <i>et al.</i> ¹⁶ Toronto, Canada	9	40	87.5	—	0 (8)*	—
Baba <i>et al.</i> ¹⁷ Hamamatsu, Japan	15	23	83	65	0.03 (1984)	0
Chapman <i>et al.</i> ¹¹ Newcastle, UK	25	40	100	—	43 (35)	—
Polkinghorne <i>et al.</i> ¹⁸ London, UK	—	72	97	90	30 (26)	15
Present study	20	32	84	81	50 (10)*	0

Values in parentheses are the numbers of individuals in each non-FAP group. *Non-polyposis colonic cancer cases. FAP, familial adenomatous polyposis; CHRPE, congenital hypertrophy of the retinal pigment epithelium

nevertheless, a longitudinal study would be needed to establish whether any or all the lesions described is congenital. This finding notwithstanding, there is considerable evidence to support the use of CHRPE as a predictive marker of FAP^{9,13,16-18}, and the present data support this.

Applying the diagnostic threshold described, a positive ophthalmic examination was found to have a sensitivity of 84 per cent. There were only two possible false-positive findings from the at-risk population and in both cases there was supporting evidence of FAP. If the at-risk individuals are considered to be controls (i.e. not carrying the affected gene), this gives a minimum specificity of 94 per cent.

Incomplete penetrance of the CHRPE phenotype within families has been reported^{10,18} and a further pedigree has been described in this study. This indicates that ophthalmic examination is worth while even in families where affected individuals have previously been found not to have diagnostic CHRPE.

Bowel examination in a young member of a family with FAP is informative only if polyps are found. A positive examination for CHRPE, however, indicates that the patient is at very high risk of manifesting the disease, with an accuracy of at least 94 per cent in the present study. Similarly, a negative examination puts the patient at a low, though not negligible, risk; this was 16 per cent in the present study. One particularly encouraging feature was the high compliance rate (97 per cent) in this form of screening.

The present findings are comparable to those from five other published studies (Table 5), although closer scrutiny shows considerable variation in CHRPE expression between the study groups^{9,11,16-18}. CHRPE expression varied from 100 to 83 per cent in affected cases, and from 0 to 43 per cent in patients without FAP. Five of these six studies found multiple bilateral lesions to be highly specific markers (specificity 95–100 per cent). Surprisingly, one series found bilateral lesions in four of 26 controls without FAP¹⁷.

Type b lesions are the most common of the four types described^{9,16,18}, but are also those most commonly seen in the population without FAP. The larger number of type b lesions seen in the older patients in this study indicates that this type of lesion may proliferate with age, particularly up to the third decade of life. This differs from previous studies of CHRPE in the unaffected population^{19,20}, and suggests that type b lesions are of a different nature. Oval pigmented lesions with a halo (type a) have been proposed as diagnostic¹⁸. These were present in 16 of 32 affected individuals in the present study. However, if these were used in isolation the sensitivity of the examination would be considerably reduced. The use of a combined set of

diagnostic criteria provided the optimum sensitivity and specificity.

A combined ophthalmic and genetic counselling clinic has been found to be beneficial, as it allows the findings and the possible consequences to be discussed at a time when the patients are receptive to the importance of screening. The variation in CHRPE expression found in different studies suggests that each centre should establish its own predictive assessment of ophthalmic examination. It is unclear to what extent such discrepancies are due to observer variation or differences in CHRPE expression within the various populations. It would seem sensible to limit ophthalmic examination in each region to a few consultants, as this will maximize their experience and provide more reproducible results.

The causative gene for FAP (*APC*) was localized to a small area on the long arm of chromosome 5 in 1987^{21,22}, since when polymorphic DNA probes closely linked to the *APC* locus have become available for predictive diagnosis in suitable families. Although this method of diagnosis is potentially more accurate than ophthalmic examination, its use is limited to individuals from large pedigrees¹⁴. The recent sequencing of the *APC* gene^{23,24} has also made direct mutation analysis possible. The value of this approach for establishing carrier status in families with FAP has yet to be determined. Early reports have suggested that there are many different mutations spread throughout the gene²⁵, which would make identification of each lesion difficult and possibly unfeasible as a screening measure. The identification of CHRPE is more widely informative than linked polymorphic markers because it can also be applied to smaller pedigrees. Unlike repeated bowel screening, both of these tests can be performed at a single hospital visit, and the accuracy of predictive diagnosis improved by combined risk analysis³. We are currently using such an approach to screening, the results being forwarded to the consultant responsible for each case. Ultimately, these measures should help to increase awareness in families and lead to improved compliance with screening in the future.

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Pouch advancement and neoleoanal anastomosis for anastomotic stricture and anovaginal fistula complicating restorative proctocolectomy

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Restorative proctocolectomy has emerged as an important advance in the surgical treatment of mucosal ulcerative colitis and familial adenomatous polyposis. It has established itself as a viable alternative in the management of patients who would otherwise require a proctocolectomy and Brooke ileostomy. The operation consists of total abdominal colectomy, proctectomy with or without mucosectomy and ileoanal anastomosis with ileal reservoir. This complex procedure leads to complications that include anastomotic stricture in about 30 per cent of patients¹⁻³. Strictured ileal pouch-anal anastomosis may arise from sepsis (causing or due to anastomotic disruption), ischaemia or excessive tension on the anastomosis⁴.

Most strictures are manageable by dilatation with a digit, bougie or proctoscope⁵. Longer and tight strictures are more difficult to manage; dilatation is either not possible or the stricture rapidly recurs. Three patients with such complex anastomotic strictures have been successfully treated by a transanal technique using pouch advancement and neoleoanal anastomosis.

Surgical technique

Before surgery, the pathology of the original specimen was re-examined to exclude Crohn's disease; if necessary, further biopsies of the ileal pouch were taken. Bowel preparation with polyethylene glycol electrolyte lavages and antibiotic prophylaxis were used. A Foley catheter was inserted to empty the bladder. The operation was performed in the prone jack-knife position under general anaesthesia, using muscle relaxants.

The anus was everted using radially placed 1/0 Dexon (polyglycolic acid; Davis and Geck, Manati, Puerto Rico) sutures through the anal verge, including the superficial portion of the internal anal sphincter and the perineum. Effacement of the lower anal canal helped to bring the strictured anastomosis into the operative field. The distance of the stricture from the dentate line was carefully noted. A lighted Ferguson anal retractor was gently inserted into the anorectal canal to enhance exposure. Isotonic saline (10 ml) was injected circumferentially into the submucosa of the anal canal at and below the stricture to improve the accuracy of depth of incision.

An incision was made at or just above the dentate line and below the strictured anastomosis. The incision was continued around the circumference of the anal canal using cautery (Figure 1). Using sharp-pointed scissors, the stricture ring and the ileal loop immediately above the anastomosis were radially dissected and raised as a circumferential flap to expose the underlying internal anal sphincter (Figure 2). Bleeding points were controlled using diathermy coagulation. Taking care not to damage the sphincter complex, cephalad dissection in this plane led to the pelvis (suprlevator space) outside the ileal pouch and superior to any preserved rectal muscular cuff (Figure 2). Using a combination of sharp and blunt dissection, the ileal pouch was mobilized circumferentially for a distance of 12 cm from the

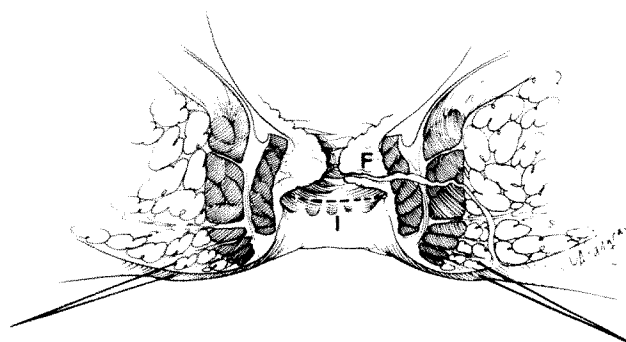


Figure 1 A circumferential incision (I) is made at or just above the dentate line and below the stricture. A fistula track (F) associated with ileal pouch-anal anastomosis may be present

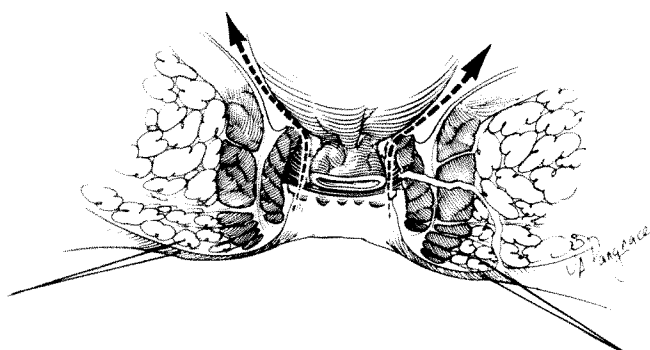


Figure 2 Plane of dissection between the ileal pouch and the underlying sphincter muscles

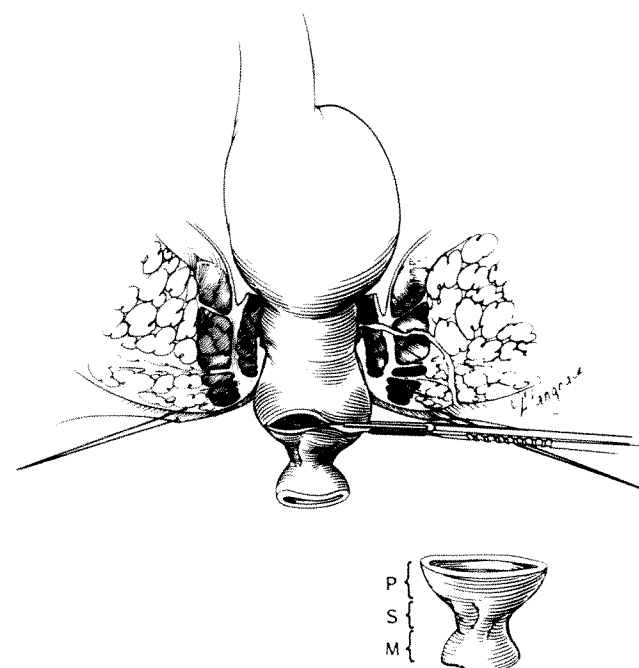


Figure 3 The mobilized pouch with the strictured segment is advanced beyond the anal verge. The stricture (S) and a cuff of the pouch (P) are excised to leave a freshened edge of the ileal pouch. M, anal mucosa (if any left)

anal verge. Tissue forceps (Babcocks) or stay sutures were applied to the edge of the stricture allowing for manipulation of the pouch, facilitating the freeing from the pouch of adhesions in the pelvis. This mobilization allowed delivery of the strictured segment and normal distal pouch beyond the anal verge (Figure 3). The stricture and a margin of the pouch were excised, leaving fresh edge of ileum level with the dentate line. The mobilized ileal pouch was then anastomosed to the anal canal at the level of the dentate line without tension using interrupted 2/0 Vicryl (polyglactin 910; Ethicon, Somerville, New Jersey, USA) sutures (Figure 4). In one case, tension on the anastomosis was relieved by placing six radial sutures between the seromuscular layer of the pouch and the lower part of the internal sphincter. A diverting stoma was not used.

The technique can be extended to repair anovaginal or anoperineal fistula associated with strictured ileoanal anastomosis, as occurred in two of the patients in this study. Similarly, it may be performed for certain complex fistulae without associated stricture. The track was identified and marked with a nylon loop. The internal opening of the track through the internal sphincter was exposed, excised in an elliptical fashion and then closed transversely with 2/0 Vicryl sutures. The mobilized ileal pouch was then advanced to cover the closed end of the track and anastomosed to the anal canal as described. The external component of the fistular track was managed by drainage using a mushroom catheter for 6 weeks, by which time drainage had ceased. The catheter was removed at a follow-up consultation.

After surgery, the patients were allowed sips of fluid for 2 days, followed by a liquid diet. A normal diet was given after 5 days. Prophylactic antibiotics were continued for 48 h.

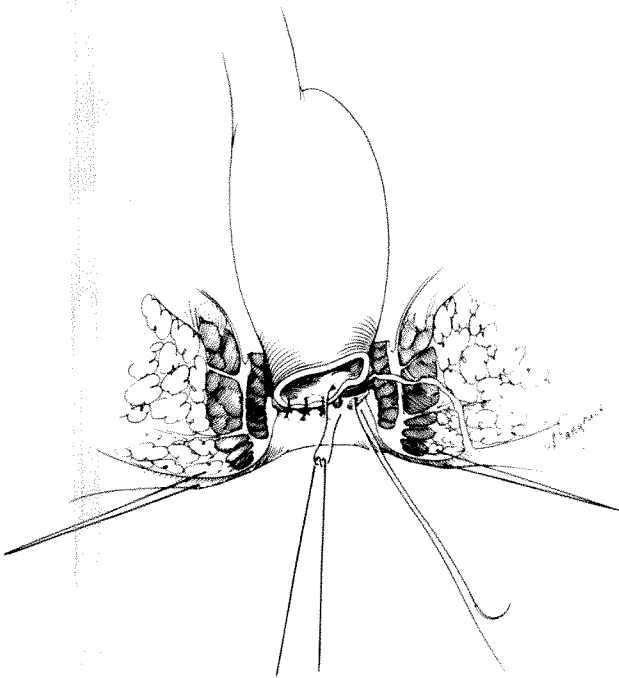


Figure 4 Anastomosis of the freshened edge of ileal pouch with the anal canal. If a fistula is present, the external component of the track should be separately drained with a mushroom catheter

Results

To date this technique has been used successfully in three patients with complicated strictured ileoanal anastomosis (Table 1). Before surgical correction, all patients had up to 20–30 bowel movements per day, frequent seepage of stool and perineal pain.

All patients derived considerable improvement from pouch advancement and neoileoanal anastomosis. All were discharged after 6 days. Patient 3 was readmitted 2 weeks later because of partial dehiscence of the anterior suture line of the neoanastomosis. This was managed by careful debridement of the cavity and freshening of the mucosal edges which were then closed with interrupted full-thickness 2/0 Vicryl sutures. At 11 months after surgery, patients 1 and 2 continued to show symptomatic improvement. The mean frequency of bowel movements was six per day. Patient 1 had good continence of stool, patient 2 continued to have minor seepage of liquid stool during the day and at night-time and needed to wear a pad. The anastomosis remained patent and could admit an adult rigid proctoscope.

Follow-up in patient 3 was only 3 months. At this stage, the anastomosis had healed with no evidence of sepsis or recurrent fistula and could admit a rigid proctoscope without difficulty. Frequency of bowel movements was six to nine per day. The patient had good continence of solid stool but minor seepage of liquid stool at night-time. All patients had relief of pain and sepsis. None had recurrent stricture up to the time of writing.

Discussion

The technique of full-thickness pouch advancement has the attraction of simplicity and safety over formal pouch reconstruction, which involves a major and difficult laparotomy. It has successfully salvaged the ileal pouch and maintained a reasonable function. Problems with intermittent seepage in patient 2 could be related to sepsis at the time of initial pouch construction or subsequent anal dilatation associated with the pouch advancement technique, even though only modest dilatation was used.

Before definitive surgery, it is important that there is no gross sepsis and that at least 3 months have elapsed to allow inflammatory oedema to settle. As a result, a diverting stoma has not been necessary in the cases reported here. This technique has also been used to treat successfully anovaginal and anolabial fistula associated with ileal pouch–anal anastomosis. Transanal endoileal advancement flap has been described⁶ for this problem but the trapdoor flap has much less distal mobility compared with the full-thickness total pouch advancement described here. In addition, the presence of an anastomotic stricture impairs exposure for fashioning a good endoileal advancement flap.

Full bowel preparation, antibiotic prophylaxis and haemostasis are important to avoid septic complications. The possibility of laparotomy with abdominal pelvic mobilization

Table 1 Patients with prior restorative proctocolectomy and ileal (J or S) pouch–anal anastomosis

Patient no.	Age (years)	Sex	Nature of stricture of IPAA	Associated anovaginal (labial) fistula	Prior treatment	Response to prior treatment	Time since pouch surgery (months)
1	35	F	Length 3 cm, calibre <8 mm	Present	Examination under anaesthesia, dilatation (thrice)	Partial and transient	18
2	42	F	Length 3 cm, calibre 5 mm	Absent	Examination under anaesthesia, dilatation (twice)	None	10
3	23	F	Length 4 cm, calibre <5 mm	Present	Examination under anaesthesia, dilatation (four times)	Partial and transient	9

All patients had cuff or pelvic abscess after pouch construction with disruption of ileal pouch–anal anastomosis (IPAA) and resultant anastomotic stricture

Surgical workshops

to augment pouch advancement was discussed with each patient before surgery but proved unnecessary. In cases where the stricture is so long (for example > 5 cm) that mobilization from the perineum alone is unlikely to be successful, then an abdominoperineal approach would be recommended as the primary procedure.

The technique described here is useful and should be included in the armamentarium of the pouch surgeon. However, it remains more efficacious to avoid complicated anastomotic stricture by meticulous preparation of the bowel ends at the time of anastomosis, ensuring a tension-free ileal pouch anal-anastomosis and prevention of pelvic sepsis.

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Brighton modification of the DeBakey aortic clamp

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Two methods of clamping the aorta in abdominal surgery exist: side clamping, utilizing the left lateral DeBakey atraumatic abdominal aortic clamp, and front clamping using a variety of devices.

The side clamp has been in use for more than 20 years. The conventional device is placed by the right-handed surgeon from the left side at the infrarenal level. Access to this clamp position is difficult, the overlying gonadal and inferior mesenteric vein adding the further hazard of bleeding while dissecting this area. Trauma to the inferior vena cava can occur from the toe of the clamp.

Front clamping, although popular, has the potential complication of aortic wall damage by malpositioning or increased torque. In addition, the first posterior midline suture is more difficult to position effectively than with a side clamp *in situ*.

To overcome these difficulties, a mirror image of the DeBakey side clamp has been developed (*Figure 1*). This limits the dissection to the space between the aneurysm sac and

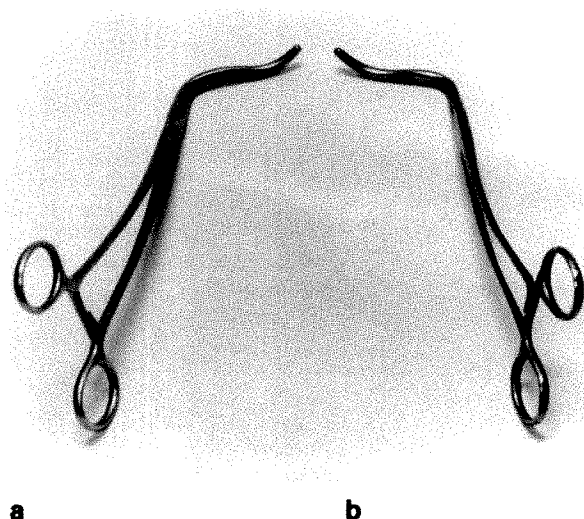


Figure 1 a Brighton modification of b DeBakey clamp

inferior vena cava with minimal left-sided clearance, allowing placement of the side clamp more safely. The proximal convexity of the clamp prevents compression of the inferior vena cava, overcoming the problem of using a Crawford clamp from the right side of the patient.

This clamp (Seward Surgical, London, UK) has now been in use in this hospital for 4 years. In more than 200 cases it has been applied safely without complication and with satisfactory results.

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Estimation of small bowel transit time following colectomy and ileal reservoir construction

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A study was carried out to evaluate the breath hydrogen test as a method of estimating small bowel transit in patients with an ileal pouch and to determine whether gut transit time influenced functional outcome. Twelve patients with an ileal reservoir and ten control subjects ingested a test meal of 400 ml chicken soup, 20 g lactulose and 50 ml dilute barium solution. Concurrent breath hydrogen testing and radiological screening was carried out until the head of the test meal reached the ileal pouch or caecum. At the time that the test meal arrived in the pouch, faecal anaerobic bacterial counts were obtained. Pouch compliance, functional capacity and anal sphincter pressures were also measured. While there was an excellent correlation between radiological and breath hydrogen measures of orocaecal transit time in controls ($P < 0.001$), no such relationship was found for oropouch transit. Four of the 12 patients with a pouch produced no hydrogen after test meal ingestion, while in two other such patients breath hydrogen peaks occurred when the head of the meal was in the jejunum. The magnitude of the breath hydrogen rise in patients with an ileal pouch correlated well with faecal anaerobic bacterial counts ($P < 0.01$). The median (95 per cent confidence interval) radiological small bowel transit time was more rapid in patients with a pouch than in control subjects: 28 (23–33) versus 72 (46–86) min ($P < 0.01$). Increased 24-h frequency of defaecation was associated with more rapid small bowel transit after ileal reservoir construction ($P < 0.01$) but correlated with neither pouch capacity nor compliance. These data show that small bowel transit time may be a determinant of ileal pouch function but that breath hydrogen estimation of gut transit time in patients with an ileal reservoir is unreliable.

Restorative proctocolectomy is now accepted as the procedure of choice in the elective surgical treatment of ulcerative colitis¹. Although the functional outcome in individual patients following ileal pouch formation is unpredictable, the best determinants of a good result seem to be a large-capacity reservoir and normal preoperative anal sphincter pressures².

Normal ileal peristalsis is altered following pouch construction and lower stool frequency is associated with less active pouch motility profiles³. Although over half of patients with an ileal pouch require intermittent use of antidiarrhoeal medication to reduce excessive stool frequency^{4,5}, the role of abnormal gut transit in ileal pouch function is uncertain. Small bowel transit time may be slower in patients with chronic ulcerative colitis than in healthy subjects⁶, but the effect of colectomy and ileal reservoir construction on this parameter is unknown.

Breath hydrogen testing is a simple, non-invasive method of assessing orocaecal transit time in healthy and diseased subjects⁷. A good correlation has been shown with γ scintigraphy in both liquid and solid meal transit^{8,9}. The increased ratio of anaerobic to aerobic bacterial counts in the ileal pouch compared with the proximal ileum¹⁰ implies that the entry of fermentable substrates into the pouch might be reflected by increased breath hydrogen levels after anaerobic bacterial metabolism in the reservoir.

The aim of this study was to determine whether the breath hydrogen technique is a valid method for the estimation of small bowel transit time and to establish whether this parameter is useful as a determinant of functional outcome following ileal pouch formation.

Patients and methods

Twenty-two subjects were studied. Twelve patients had had an ileal reservoir formed a median of 20 (range 12–33) months previously. The other ten subjects were recruited from surgical outpatient clinics, had no abnormal gastrointestinal symptoms, and acted as controls. All patients gave informed consent and the study was approved by the Central Birmingham Ethical Committee.

Transit time

Small bowel transit time was determined by the technique of serial exhaled breath hydrogen sampling¹¹. After an overnight fast of at least 18 h, and standard mouth hygiene¹², a series of basal exhaled breath hydrogen samples was collected¹³. After this basal period, a standard test meal of 400 ml chicken soup (H. J. Heinz, Hayes, UK; 255 kcal) and 30 ml (20 g) lactulose (Duphalac; Duphar, Southampton, UK) was ingested. This meal has previously been shown to produce a breath hydrogen rise with a mean individual coefficient of variation of 11 per cent in eight normal individuals who ingested it on three separate occasions¹⁴. In the present study, the meal contained an additional 50 ml dilute barium sulphate suspension (see below).

After ingestion of the meal breath samples were collected at 5-min intervals and then every 2 min once values became raised. A sustained rise in breath hydrogen by more than twice the mean baseline value was taken to indicate arrival of the head of the meal in the pouch or caecum. In earlier studies this value provided a simple, reproducible endpoint that reduced erroneous interpretation arising from baseline variation¹³.

Breath hydrogen concentration was measured using an electrochemical technique. The hydrogen meter is accurate to within 2 per cent and has a repeatability of ± 1 p.p.m. (Gas Measurement Instruments, Renfrew, UK). It was calibrated before each study with a known source of hydrogen (concentration 96 p.p.m.).

To determine whether any rise in breath hydrogen in patients could have resulted from bacterial fermentation in the upper gut, rather than rapid oro-caecal or oropouch transit, all subjects ingested 50 ml dilute barium solution (30 per cent weight:volume with water) mixed with the test meal. Serial fluoroscopic examinations of the passage of barium were then made together with breath hydrogen sampling to determine whether the onset of the rise in hydrogen concentration preceded or followed the arrival of the head of the barium meal at the pouch or caecum.

The ileal pouch was localized in each patient before the study using a balloon attached to a transanal catheter into which dilute barium was infused. After radiographic localization on anterior and lateral images and application of skin markers, the barium was drained and the catheter removed. The caecum was readily identified on radiographic screening in each control. The number of radiographic exposures was kept to a minimum.

Pouch bacteriology

At the time that the head of the meal arrived in the pouch, fresh faecal samples were obtained from each patient. A 1-g sample of faeces was immediately mixed with 9 ml glycerol infusion broth. Duplicate 1-ml samples of faecal suspension were then snap-frozen at -70°C and stored at this temperature¹⁵ for 1 week. At the time of bacteriological processing all specimens were rapidly thawed in a water bath at 37°C and the paired samples pooled. Serial faecal suspension dilutions were inoculated on to a range of anaerobic media^{16,17}.

The anaerobic organisms isolated were identified by the morphological appearance of the colonies, microscopic appearance after Gram staining, and standard biochemical testing¹⁸. The total anaerobic bacterial count was expressed as colony-forming units (c.f.u.) per gram of ileal stool.

Clinical data

All patients kept a diary of the frequency of defaecation in the 24 h during which the study took place. No patient ingested any other food or calorie-containing liquids apart from the test meal in this period. Episodes of faecal soiling sufficient to require use of a pad were recorded. Inability to defer defaecation for >30 min was defined as urgency and recorded.

Pouch endoscopy was performed before the study to exclude acute reservoir ileitis. Measurements of functional pouch capacity and compliance were made using a water-perfused balloon catheter¹⁹. Maximum resting and incremental squeeze anal pressures were measured using a closed water-filled balloon probe and a station pull-through technique²⁰.

Statistical analysis

Grouped data were expressed as the median (95 per cent confidence interval). Comparisons between groups were made using the Wilcoxon rank test for unpaired data. Association between variables was studied using the Spearman rank correlation coefficient (r_s). Significance was assumed at a two-tailed P value of <0.05 .

Results

The two groups were matched for age and sex. Of the 12 patients with an ileal reservoir, six had a W pouch and six a J pouch. The W and J pouch groups were matched for diagnosis: ulcerative colitis (four patients), familial adenomatous polyposis (one) and slow transit constipation (one). No patient in this study had an ileal resection >5 cm and none had endoscopic evidence of pouchitis.

There was a strong correlation between breath hydrogen and radiological assessment of oro-caecal transit in control subjects ($r_s = 0.95$, $P < 0.001$). In contrast, there was no correlation between breath hydrogen and radiological evaluation of oropouch transit ($r_s = -0.23$, P not significant). In four of the 12 patients with a pouch no hydrogen was produced following ingestion of the test meal. In a further two patients breath hydrogen peaks occurred when the head of the meal was in the jejunum.

There was a significant correlation between pouch faecal anaerobic bacterial counts and breath hydrogen rise above baseline on arrival of the meal in the pouch ($r_s = 0.68$, $P < 0.01$). The four patients who produced very little breath hydrogen following test meal ingestion had low counts of tota-

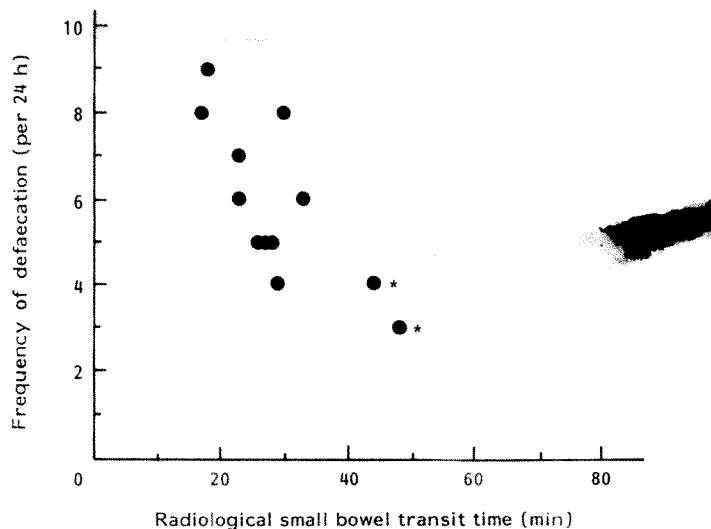


Figure 1 Correlation between radiological transit of the head of the meal and 24-h frequency of defaecation in patients with an ileal pouch. *Two patients who had undergone colectomy and ileal reservoir construction for constipation. $r_s = -0.74$, $P < 0.01$

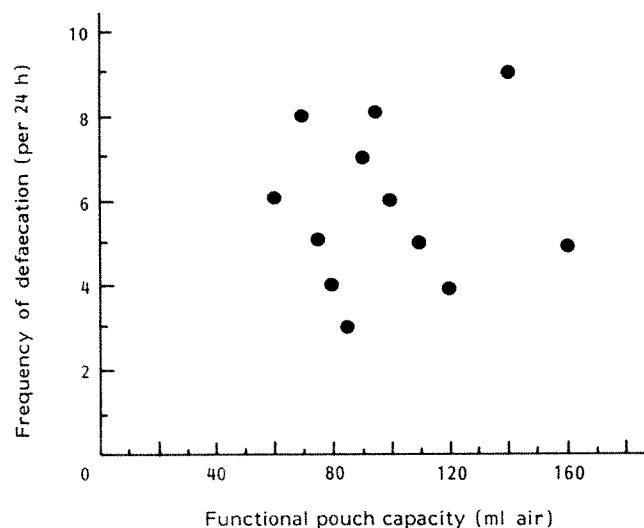


Figure 2 Functional reservoir capacity and 24-h defaecation frequency in patients with an ileal pouch. $r_s = 0.18$, P not significant

anaerobic bacteria in the pouch stool (fewer than 1.0×10^8 c.f.u. per g).

There was a significant correlation between an increased 24-h defaecation frequency and more rapid radiological transit of the head of the meal in patients with a pouch ($r_s = -0.74$, $P < 0.01$; Figure 1). The two patients with slow transit constipation had the lowest 24-h frequency of defaecation and the slowest radiological transit time. There was no difference in radiological transit time between patients with a J pouch and those with a W pouch (27 (18–44) versus 26 (17–48) min). Radiological small bowel transit time was more rapid in patients with a pouch than in control subjects (28 (23–33) versus 72 (46–86) min, $P < 0.01$).

Neither pouch capacity nor compliance was related to 24-h defaecation frequency in this study (Figures 2 and 3). In contrast, the four subjects who experienced episodes of nocturnal faecal soiling sufficient to require use of a pad had the lowest resting anal pressures (Table 1). However, no patient documented any periods of urgency and all had recordable squeeze anal pressures.

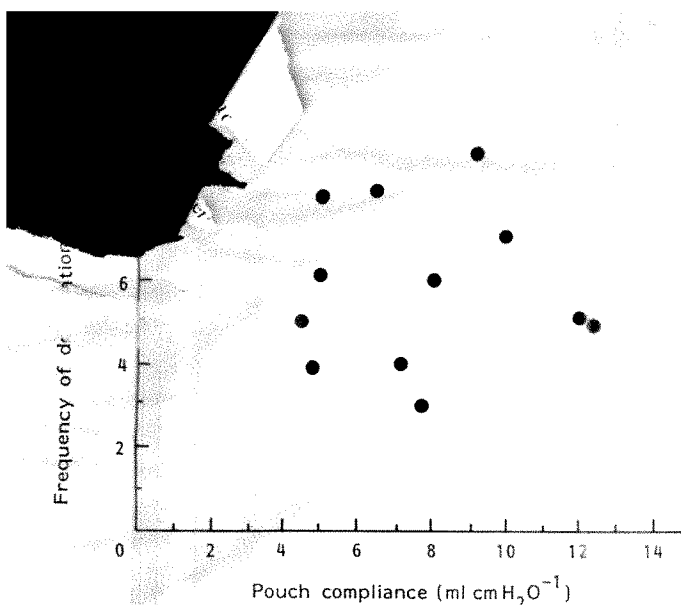


Figure 3 Reservoir compliance and 24-h defaecation frequency in patients with an ileal pouch. $r_s = 0.12$, P not significant

Table 1 Soiling, urgency and anal sphincter pressures in 12 patients with an ileal pouch

Patient no.	Soiling		Urgency	Anal sphincter pressure (cmH ₂ O)	
	Daytime	Night-time		Rest	Squeeze increment*
1	—	—	—	130	115
2	—	—	—	110	125
3	—	—	—	130	210
4	—	—	—	110	150
5	—	+	—	85	100
6	—	+	—	80	135
7	—	—	—	100	215
8	—	—	—	135	190
9	—	+	—	70	115
10	—	+	—	75	100
11	—	—	—	125	140
12	—	—	—	105	120

*Calculated using the formula:

incremental squeeze pressure = total squeeze pressure — resting pressure

Discussion

This study has shown that small bowel transit time is markedly reduced in patients with an ileal pouch compared with that in normal subjects. Breath hydrogen sampling was found to be unsuitable for the measurement of gut transit in patients with an ileal reservoir.

The method of breath hydrogen estimation was designed to ensure standardization and to facilitate reproducibility both between and within patients. Lactulose was combined with a standardized liquid meal²¹ and the early breath hydrogen peak abolished by use of an antibacterial mouthwash. Extraintestinal influences on breath hydrogen estimation such as smoking, hyperventilation, recent food intake, exercise, body posture and lactulose dose were also standardized^{13,22}. While a lactulose and chicken soup meal is not physiological, it does fulfil some of the criteria of a useful marker for measuring gut transit²³. Previous studies by this unit have confirmed the reported accuracy^{24,25} of breath hydrogen sampling as a measure of small bowel transit time of this meal in normal subjects.

There are several explanations for the lack of correlation between radiological and breath hydrogen estimates of small bowel transit in the patients with a pouch. The causes of a negative breath hydrogen test include an acidic micro-

climate^{26,27}; recent work has shown that pouch pH is predominantly acidic²⁸. Alternatively, any hydrogen produced may be rapidly metabolized by local luminal bacteria²⁹. However, the most likely reason is the presence of small numbers of hydrogen-generating anaerobic bacteria^{30–32}. The four patients with a pouch who produced no hydrogen had low counts of anaerobic pouch bacteria.

The early jejunal peaks of breath hydrogen in two other patients with a pouch were probably caused by jejunal bacterial overgrowth, although no direct measure of bacterial counts in the jejunum was made. It may be relevant that these two patients had the highest frequency of defaecation among the patients with a pouch and that jejunal bacterial overgrowth is associated with poor function in patients with an ileal reservoir³³.

It is unlikely that these two patients had such rapid oropouch transit that the appearance of the head of the meal in the pouch was missed. The serial fluoroscopic examinations showed barium in the jejunum only after the peak of breath hydrogen.

An interesting but expected finding was that of slow small bowel transit and low 24-h defaecation frequency in the patients with an ileal pouch formed for slow transit constipation. This study has also shown a correlation between increased 24-h frequency of defaecation and more rapid radiological transit of the head of the test meal in patients with a pouch. However, these findings must be interpreted with caution. Barium sulphate as a marker has several shortcomings as it mixes poorly with gastric contents and may itself influence gut transit. The barium solution used in this study was dilute and was well mixed in with the test meal before ingestion. However, other studies have shown poor reproducibility within and between individuals and the method is not physiological^{34,35}. Despite these reservations, the absence of the salvage function of the colon after ileal pouch construction may mean that reduced radiological small bowel transit time of the head of this test meal is a potentially important mechanism of diarrhoea formation in these patients^{36,37}.

This hypothesis is further supported by the absence of an association between functional pouch capacity or compliance and 24-h defaecation frequency. This finding is at variance with others² and may be due to the similar lengths of ileum used for both the W and J pouches in this study¹⁹. However, this work has confirmed the importance of an intact anal sphincter as a determinant of acceptable faecal continence in patients with an ileal pouch.

It is important to emphasize that the 24-h defaecation frequency recorded in this paper represented a single response to an osmotic load on the study day. Longer term studies would be needed to determine correlations with normal stool frequency in patients with a pouch.

The ileal brake mechanism has been shown to be active in some patients with an ileal pouch and gastric emptying is also unaffected by ileal reservoir formation³⁷. Colectomy and the absence of the ileocaecal valve probably account for the rapid intestinal transit in these patients³⁸.

In conclusion, this study has shown that breath hydrogen sampling is an unreliable measure of small bowel transit time in patients with an ileal reservoir. However, small bowel transit may be a determinant of ileal pouch function and further studies using alternative techniques with measurement of gastric emptying and movement of the bulk of an ingested meal are now required³⁹.

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Subcutaneous rectal stump closure after emergency subtotal colectomy

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Subtotal colectomy with preservation of the rectum is the favoured procedure in acute surgery for severe colitis. It allows for careful assessment of colonic histology and the possibility of a subsequent restorative procedure. The management of the distal bowel is controversial: if closed and left in the pelvis there is a risk of perforation and it may be difficult to locate^{1,2}.

A mucus fistula allows external drainage and theoretically restricts any sepsis to an extraperitoneal site, and makes subsequent location much easier. It may be sited away from the main incision² or at the distal end of the incision itself^{3,4}. It does, however, impose a second stoma on a patient who may already have difficulties accepting an ileostomy. Blood and mucus discharging from the fistula may at times produce significant problems, although in some cases the discharge may be very light and the fistula will occasionally close spontaneously.

As an alternative to a mucus fistula, the rectal stump can be closed at the time of acute surgery, and sited subcutaneously at the caudal end of the abdominal incision⁵. The skin at the lower end of the abdominal wound may be left open to heal secondarily over this 'closed mucus fistula', or primary closure of the entire wound can be performed. A second stoma is not required and the dangers of perforation are avoided; it can also be easily located at the time of further definitive surgery. While most authors refer to the 'rectal stump', in practice surgeons should divide the distal sigmoid colon to ensure that there is no tension on the mucus fistula; the term rectal stump is thus something of a misnomer.

Patients and methods

A study was performed at the John Radcliffe Hospital, Oxford, and the Royal Hospital, Wolverhampton. A total of 32 consecutive patients underwent acute subtotal colectomy. The indications for surgery were failure of medical management, perforation, toxic megacolon, peritonitis and haemorrhage. In four patients the distal bowel was closed with 3/0 Vicryl (Ethicon, Edinburgh, UK). The remaining 28 underwent closure using a GIA50 or 60 stapler (Auto Suture, Ascot, UK). In five patients the stapled stump was also oversewn using 3/0 Vicryl. The stapled mucus fistula was then sewn in a subcutaneous

Subtotal colectomy with preservation of the rectum is now the procedure of choice for patients with severe colitis requiring emergency surgery. The use of subcutaneous 'rectal closure' when the retained distal bowel is placed at the caudal end of the abdominal incision in the subcutaneous or fascial layer is studied. An anal catheter may be placed to drain the rectum. Thirty-two patients (14 men, 18 women) of mean age 33 (range 17–77) years with severe inflammatory bowel disease (29 ulcerative colitis, one Crohn's disease, one indeterminate colitis, one Campylobacter colitis) underwent emergency colectomy with subcutaneous rectal stump closure. Twenty-three stumps were closed with staples, four sutured and five by both staples and sutures. Complications developed in seven patients (22 per cent), of which two required surgical intervention. One significant wound infection was treated successfully with a course of antibiotics. Three minor wound infections did not require specific treatment. The rectal stump was always readily located at the time of restorative surgery. This technique is recommended as a simple and safe alternative to an open mucus fistula provided that surgeons adhere to standard surgical principles; in particular the distal bowel should not be brought out into the wound under tension.

location to the deep fascia at the caudal end of the main abdominal incision. In the 17 patients at Wolverhampton the lower end of the abdominal incision was left open, while in the 15 at Oxford primary closure of the incision over the closed distal bowel was performed. In Oxford an anal catheter was routinely placed to drain the rectum.

Details were recorded of age, sex, duration of disease and acute symptoms, the use of steroids, indications for surgery, histological diagnosis and the technique of rectal stump and wound closure. Morbidity was assessed in terms of wound complications (infection, dehiscence) and intra-abdominal complications (abscess, peritonitis).

Results

Thirty-two patients (male:female ratio 14:18) of mean age 33 (range 17–77) years underwent subtotal colectomy with superficial siting of the closed rectal stump. Histological diagnoses were ulcerative colitis ($n = 29$), Crohn's disease ($n = 1$), indeterminate colitis ($n = 1$) and *Campylobacter* colitis ($n = 1$). Disease had been present for >1 year in 11 patients, four had had symptoms for <1 year and in 17 patients the acute episode was the first attack. Of the patients who had presented before the acute episode which required surgery five had not been receiving steroids; one had been on maintenance steroids for <1 month, six for <1 year and one for >1 year. Intensive medical treatment before emergency surgery occurred in 21 patients; two received only preoperative cover with intravenous hydrocortisone. The most frequent indication for surgery was failure of symptoms to resolve on medical management ($n = 28$), and two of these patients had significant colonic bleeding. There were five patients with toxic megacolon; two of these suffered perforation, one without evidence of dilatation. Twenty-three stumps were closed with staples, four with sutures and five with both staples and sutures. There were no postoperative deaths.

Morbidity

Complications occurred in seven patients (22 per cent) (Table 1): four (12 per cent) required intervention; two (6 per cent) required early reoperation. There were no deaths. In Oxford, postoperative complications occurred in three of 15

Table 1 Summary of patients with complications

Patient no.	Age (years)	Sex	Duration of disease	Duration of acute symptoms	Maintenance steroids	Intensive steroids	Indications for surgery	Histology	Rectal stump closure	Wound closure	Morbidity
Oxford											
1	55	M	3 weeks	3 weeks	Nil	3 days	Toxic megacolon	UC	Stapled	MN	Wound infection
2	28	M	5 years	4 days	1 week	5 days	Failed medical therapy	UC	Stapled	MN	Wound infection
3	54	M	14 years	3 weeks	Nil	13 days	Failed medical therapy	UC	Oversewn	PDS, PDS	Wound dehiscence Necrotizing fasciitis
Wolverhampton											
4	33	F	12 months	17 days	Nil	18 days	Failed medical therapy	UC	Stapled	Nylon	Minor leak from stapled rectal stump
5	41	F	4 weeks	4 weeks	Nil	4 days	Failed medical therapy	UC	Stapled	Nylon	Persistent discharge from rectal stump
6	25	F	3 weeks	3 weeks	Nil	9 days	Failed medical therapy	UC	Stapled	Nylon	Pelvic and paracolic sepsis
7	43	M	4 years	4 weeks	Nil	11 days	Failed medical therapy	UC	Stapled	Nylon	Minor leak from stapled rectal stump

UC, ulcerative colitis; MN, monofilament nylon; PDS, polydioxanone sutures

patients (20 per cent), of which one (7 per cent) required surgical intervention. One wound swab grew *Pseudomonas aeruginosa* but no specific antibiotic treatment was required and the wound had healed by follow-up at 6 weeks. One patient developed a discharge at the lower end of the wound and was started on a course of amoxycillin and metronidazole. The infection had resolved by the time of a restorative operation 3 months later. One patient was a long-standing insulin-dependent diabetic who received intensive steroids for 13 days before acute surgery. He made an excellent recovery and was discharged 10 days later. He was, however, readmitted 3 weeks after surgery with the rectal stump open and necrotizing fasciitis of the lower abdominal wall extending to the right flank and back and down to the scrotum. Although some pus was noted in the pelvis at initial laparotomy the major feature was that of an extraperitoneal infection. A catheter was inserted to drain the open rectal stump and extensive debridement of necrotic tissue carried out. In total, seven visits to the operating theatre were required over the next 3 weeks. Virtually complete debridement was achieved after the first two procedures, and only repacking of wounds was performed thereafter until primary closure of his scrotal, abdominal, back and flank wounds was achieved. The patient was discharged 1 month after readmission and remains well. The wound swabs grew *Escherichia coli* and mixed anaerobes sensitive to a combination of cefuroxime and metronidazole, which the patient received for 4 weeks from the day of readmission.

In Wolverhampton, four patients (24 per cent) developed complications, of which only one was significant and required emergency intervention for pelvic and paracolic sepsis; the pus was drained and the patient made a good recovery. Three patients developed a leak from the stapled fistula; two were minor, of which one healed spontaneously and one persisted until definitive surgery to the rectum. In the third patient persistent purulent discharge led to proctectomy 8 months after acute subtotal colectomy.

Discussion

Subtotal colectomy with rectal preservation has superseded proctocolectomy as the procedure of choice in emergency surgery for severe colitis. The disadvantages of proctectomy in the acute situation include further blood loss and pelvic sepsis^{1,3}. Between 1975 and 1986, 11 proctocolectomies and 62 subtotal colectomies were performed urgently at St Mark's Hospital, London³. The mortality rate was 9 per cent for proctocolectomy and <2 per cent for subtotal colectomy. Recent studies describing total colectomy with excision of the rectum leaving only the anal canal *in situ* in anticipation of a

reservoir procedure, have been shown to be fraught with complications^{6,7}.

Factors associated with a poor prognosis and increased postoperative complications include advanced age^{8,9} and severity of the colitis, particularly toxic megacolon with perforation^{9,10}. The influence of steroid therapy remains uncertain; prolonged use of steroids has been implicated in the development of postoperative complications by some¹⁰ but discounted or deemed inconclusive by others^{4,8,11}.

Significant problems may arise in the retained rectum, especially bleeding, so that urgent secondary proctectomy is sometimes required^{8,11,12}. In most cases non-surgical management is adequate^{3,4,12}; however, this raises the question of where best to site the rectal stump. It is accepted that closing the rectal stump within the pelvis carries the risk of serious pelvic sepsis and renders later surgery difficult^{1,2}. The reported mortality rate for such a procedure has been 8.3–25 per cent^{11,12}, but the number of patients involved has been very small.

The favoured procedure has been the mucus fistula. Lee and Truelove² recommended that the fistula should be sited in the left iliac fossa away from the main incision to avoid major wound infection; others prefer to site it in the caudal end of the abdominal incision^{3,4}. Using the latter technique Flatmark *et al.*¹² reported 63 acute cases with no deaths; two patients did require urgent proctectomy for persistent disease, but there were no other significant problems and no wound complications. Albrechtsen *et al.*⁴ reported a series of 132 patients, of whom 120 underwent urgent subtotal colectomy with a mucus fistula sited in the wound. Seven deaths (5.8 per cent) occurred in this group of 120, none of which was related to the siting of the rectal stump. Non-fatal complications developed in 53 (40.2 per cent) of the 132 patients, and included 28 cases (21.2 per cent) of wound sepsis, four cases (3.0 per cent) of wound dehiscence and 11 (8.3 per cent) of intra-abdominal abscess. Other series of acute subtotal colectomy have reported mortality rates of 11–42 per cent and non-fatal complication rates of 20–51 per cent^{3,8,10,13,14}. However, direct comparison of these figures with those in the present study is not possible; the site of the rectal stump is not always indicated and complication rates include those unrelated to the rectal stump.

Despite its advantages, a mucus fistula still involves forming a second stoma. Abdominal drainage often continues and may undermine the faceplate around the stoma, resulting in a poor seal¹. It has been suggested that secondary subcutaneous closure of the rectal stump can be performed after the initial acute inflammation has subsided¹. We support Motson and Manche's proposition⁵ that subcutaneous closure of the distal bowel can be carried out safely at the initial acute operation.

The skin overlying this can be closed or left open. In the present series of 32 patients undergoing this procedure there were no deaths and only two developed significant complications. The first, who developed necrotizing fasciitis, was a long-standing insulin-dependent diabetic and had received intensive steroid therapy for 13 days before colectomy. The other significant complication was in a patient who developed intra-abdominal sepsis. This was presumed to be due to leakage from the mucus fistula, but equally it could have resulted from intraoperative contamination.

Although the complication rate in this study was low, the two patients who required surgery had serious problems and the need to ensure that the retained rectosigmoid has a good blood supply and that it is laid at the lower end of the wound without tension must be emphasized. Closure of the mucus fistula must be as careful as possible. A GIA90 (Auto Suture) or PLC60 (Ethicon) stapler has an advantage over the GIA50 when the bowel is thickened and oedematous; oversewing the stapled end where the bowel is particularly soft and friable provides a second layer of closure and added safety.

This technique is easily performed, is relatively safe and spares the patient a second stoma. It also facilitates subsequent surgery by allowing easy location of the stapled fistula lying in a subcutaneous site at the time of further surgery.

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Case report

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Embolization of superior haemorrhoidal artery in the management of life-threatening rectal bleeding

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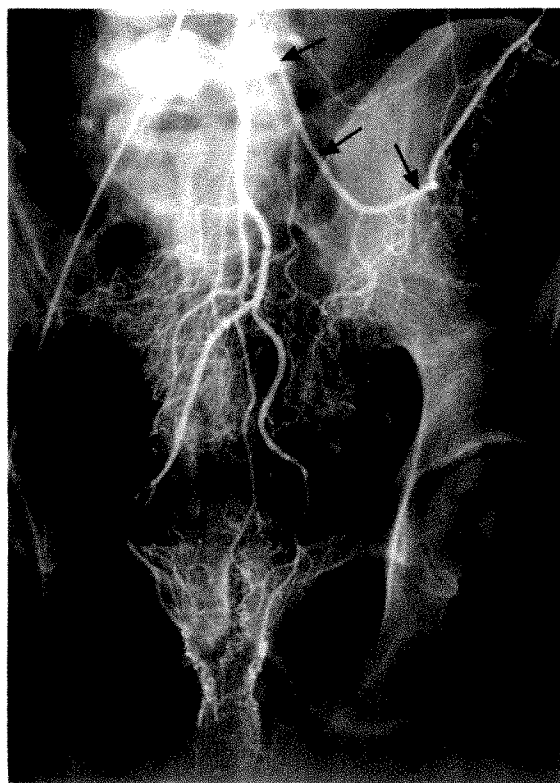
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Angiography after proctosigmoidoscopy in the management of patients with acute lower gastrointestinal bleeding is now well established for localizing the site of such bleeding. The role of angiography in the control of lower gastrointestinal bleeding remains poorly defined. This report describes two patients with life-threatening rectal bleeding that was successfully stopped by selective embolization of the superior haemorrhoidal artery.

Patient 1

A 64-year-old man presented with bright red rectal bleeding 4 weeks after triple coronary artery bypass graft surgery from which he had made an uncomplicated recovery. The bleeding was severe enough to

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cause hypovolaemic shock which required urgent resuscitation and blood transfusion (5 units). Sigmoidoscopy under epidural anaesthesia revealed a large, solitary, bleeding rectal ulcer, around which deep ligatures were passed to control the bleeding. A further massive rectal bleed occurred the next day and inferior mesenteric arteriography via the femoral artery was performed. Although this study was normal, it was decided to embolize the superior haemorrhoidal artery. Using a coaxial catheter technique and a 3-Fr Teflon (Du Pont, Stevenage, UK) catheter, the superior haemorrhoidal artery was selectively catheterized. With the catheter tip safely beyond the sigmoid branches, the superior haemorrhoidal artery was embolized using multiple Gelfoam particles (Ferrosan, Denmark), approximately 1 mm³ in size and injected a few at a time (Figure 1). This successfully prevented further rectal bleeding. The patient had no further bouts of rectal bleeding and no clinical evidence of bowel ischaemia. He died from cardiac disease 4 months later.

Patient 2

A 76-year-old man presented with intermittent rectal bleeding and prolapse. A large rectal villous adenoma was excised locally under general anaesthesia. After this there was severe rectal bleeding from the operation site which required urgent transfusion of 4 units of blood. Two attempts were made in the next 24 h to control this bleeding with ligatures, without success. Selective inferior mesenteric arteriography was performed, which demonstrated localized extravasation of contrast medium from the superior haemorrhoidal artery (Figure 2). This artery was then subselectively catheterized and embolized. Colonoscopy performed later showed no evidence of bowel ischaemia but revealed

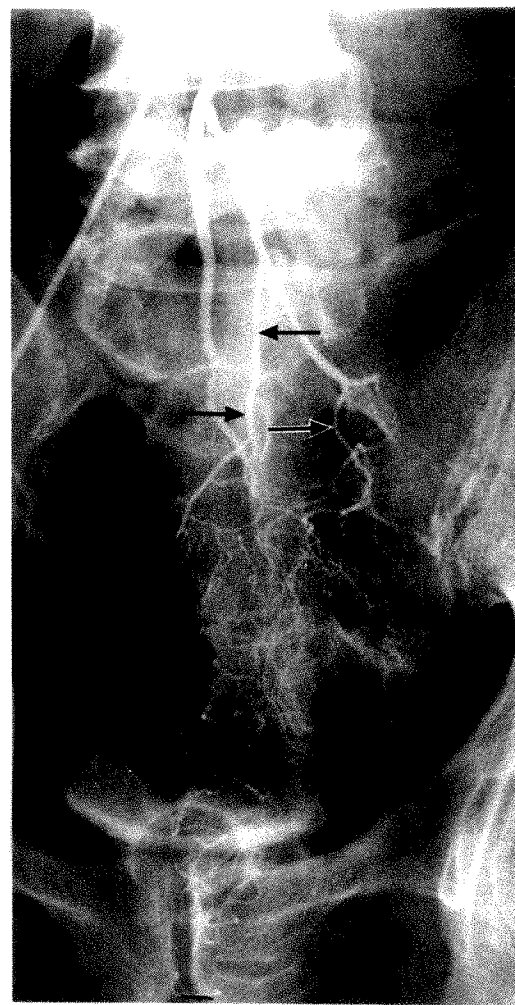


Figure 1 **a** Selective inferior mesenteric arteriogram. Note the superior haemorrhoidal branch supplying the rectum and extending to the anus. A large sigmoid branch (arrows) arises more proximally. **b** Arteriogram following embolization of the superior haemorrhoidal branch with Gelfoam particles. The coaxial catheter is still in the superior haemorrhoidal artery, but this now shows no distal flow. Some contrast refluxes and fills the sigmoid division and two of its more proximal branches (arrows)

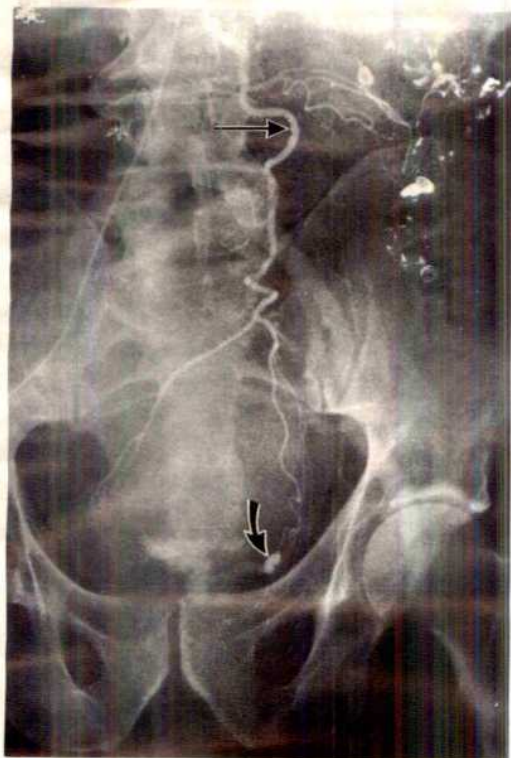


Figure 2 Selective inferior mesenteric arteriogram. Note the localized extravasation of contrast medium from a branch of the superior haemorrhoidal artery (curved arrow). The tip of the coaxial catheter was subsequently placed in the superior haemorrhoidal artery (at point of arrow →) distal to the proximally arising sigmoid branches. The origin of the inferior mesenteric artery is just above the top of the film

a further tumour in the sigmoid colon. Extended abdominoperineal excision of the rectum was undertaken 4 weeks after the first operation. The patient remains alive and well 2 years later.

Discussion

Angiography has a well defined role in the management of patients with gastrointestinal bleeding. It is valuable in identifying the site of bleeding and has been used successfully to achieve haemostasis by either percutaneous arterial infusion of vasoconstrictor agent or transcatheter embolization and occlusion of the bleeding artery¹. Embolization has traditionally been avoided below the ligament of Trietz because there is not the same potential for collateral circulation as above this point. Experience of embolization in lower gastrointestinal bleeding is therefore limited, and isolated cases of superior²⁻⁵

and inferior^{4,6} mesenteric artery embolization have been reported. In one large review of 18 patients undergoing superior mesenteric artery embolization (jejunal or ileal branches), four cases of small bowel ischaemia were reported⁷. Others have reported five cases of large bowel ischaemia following embolization for colonic bleeding in 44 patients^{8,9}. It is clear that careful, cautious and selective embolization is needed.

Visceral embolization has been made easier by improvements in catheters and techniques, in particular by coaxial embolization, which involves passing a smaller catheter through the lumen of a larger catheter to reach more distal locations, thus minimizing the risk of trauma and spasm in these small arteries.

The rectum has a rich blood supply from the inferior mesenteric and internal iliac arteries, and the risk of ischaemia following embolization should be low.

This paper has described two patients in whom life-threatening rectal bleeding was successfully controlled by selective embolization of the superior haemorrhoidal artery after conventional surgical methods had failed. Bowel ischaemia was encountered in neither case. Embolization of the superior haemorrhoidal artery to control severe rectal bleeding is an effective and safe solution to what can be a formidable problem, especially in patients at poor risk.

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Elective *versus* emergency surgery for patients with colorectal cancer

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A prospective study of 570 patients presenting with colorectal cancer over a 5-year period was undertaken. Of these, 363 were admitted electively and 207 presented as emergencies. The outcome following elective admission was more favourable than after emergency admission. In the elective group the proportion of resected tumours was greater (77 versus 64 per cent, $P < 0.001$), the operative mortality rate lower (9 versus 19 per cent, $P < 0.001$) and the 5-year disease-related survival rate higher (37 versus 19 per cent, $P < 0.001$). These differences may relate to the greater resection rates in the elective situation. Results of surgical intervention might be improved if emergency colorectal operations were undertaken by surgeons with more experience of this type of surgery.

In 1989 almost 2000 deaths in Scotland were attributed to colorectal cancer¹. Approximately 20 per cent of patients with colorectal carcinoma present as emergencies²⁻⁵. Retrospective studies have demonstrated a poor prognosis associated with emergency surgery compared with elective treatment^{3,4}, but it is not clear whether patients who present as emergencies have more advanced disease.

To exclude the potential bias inherent in retrospective analyses, a prospective study of all patients presenting with colorectal cancer at this hospital was initiated in 1974. The aim of this analysis was to compare the outcome of elective and emergency colorectal surgery and examine the scope for improvement in patient management.

Patients and methods

All patients presenting with a clinical diagnosis of colorectal cancer between 1 January 1974 and 31 December 1979 were included in the study. Prospective data recorded included age, sex, site of tumour⁶, the nature of surgery, and postoperative mortality. Admissions were classified as elective or emergency. Assessments of the extent of intraperitoneal tumour spread and presence of liver metastases were based on findings at operation⁷. Particular attention was paid to the extent of extramural local tumour spread to adjacent tissues or organs, such as invasion of mesentery, abdominal wall, small bowel or perirectal fat. The extent of tumour spread was assessed by Dukes' classification, based on histological examination of the resected specimen⁸.

Patients were deemed to have undergone a curative resection if the surgeon considered that there was no macroscopic residual tumour once resection had been completed. Resection carried out in the presence of distant metastases, or where inadequate local clearance was achieved, was classified as palliative. Patients in the palliative diversion group were treated with a proximal defunctioning colostomy or bypass, the primary tumour being left *in situ*. Operative mortality included all deaths occurring within 30 days of surgery.

Patients were followed every 3 months for 2 years at a designated colorectal cancer clinic, at 6-month intervals for a further 3 years and thereafter annually until the tenth anniversary or death. The dates of first detected recurrence and death were recorded. Estimations of the percentage of patients alive at 2 and 5 years were made using life-table techniques⁹.

Statistical comparisons were carried out using the χ^2 test. To compare the operative mortality and survival rates of patients presenting electively or as emergencies, recognizing that patients differ in terms of presenting characteristics, a two-step approach was used. First, predictive factors for operative mortality were identified using the χ^2 test without reference to the nature of the admission. Second, the corrected operative mortality rate was calculated using logistic regression analysis¹⁰ incorporating the factors identified.

Significant predictive factors for survival were identified using Cox's proportional hazards method¹¹ without reference to the type of admission. Elective and emergency admissions were then compared using this model, incorporating the factors identified above. Cox's

model produces as a measure of output the relative hazard ratio, which indicates the time-specific mortality rate for patients admitted as emergencies compared with those admitted electively. Values >1 indicate a higher mortality rate than average for emergency cases. The above procedure was carried out for all patients combined and for those undergoing curative resection, palliative resection or palliative diversion.

Results

Patients

During the study period 645 patients presented with colorectal cancer², of whom 75 were omitted from this analysis. Reasons for exclusion were: mode of admission not recorded ($n = 37$); patient transferred from another hospital ($n = 23$); and patient admitted directly from the outpatient clinic ($n = 15$). The analysis was therefore based on a total of 570 patients, of whom 207 (36 per cent) were admitted as emergencies.

The proportion of patients ≥ 75 years old was higher among emergency presentations (29 versus 17 per cent; Table 1). The incidence of previous cardiorespiratory disease was similar in the two groups.

A greater proportion of rectal cancer was present in patients treated electively (44 versus 22 per cent) and an excess of splenic flexure lesions in the emergency group (12 versus 2 per cent).

Intestinal obstruction was a presenting feature in 82 patients of the emergency group; three presented with perforation and 34 with haemorrhage. More patients with no local or distant tumour spread were present in the elective group (49 versus 38 per cent). Distribution according to Dukes' classification, where known, was similar for both groups, but tumours were unstaged in a higher proportion of patients in the emergency group.

Most of the electively admitted patients undergoing surgery (72 per cent) were treated by consultant surgeons. Of patients admitted as emergencies undergoing surgery >48 h after admission, 64 per cent were operated on by a consultant surgeon; consultants were present at only 45 per cent of emergency procedures occurring within 48 h of admission.

Resection rate

The rate of resection was higher in the elective than in the emergency group (77 versus 64 per cent, $P < 0.001$; Table 2). There was a higher incidence of resection in all age groups in the elective group (Table 3). Those undergoing elective surgery were more likely to have their tumour resected whether it was situated in the right colon (87 versus 66 per cent), left colon (78 versus 61 per cent) or rectum (72 versus 67 per cent).

The relationship between the extent of disease and treatment is shown in Table 4. Patients with no manifest spread underwent

Table 1 Characteristics of 570 patients at presentation undergoing emergency or elective colorectal surgery

	Emergency surgery (n = 207)	Elective surgery (n = 363)
Age (years)		
< 55	40 (19)	68 (19)
55-64	41 (20)	106 (29)
65-74	66 (32)	127 (35)
≥ 75	60 (29)	62 (17)
Sex ratio (M:F)	95:112 (46:54)	190:173 (52:48)
Cardiorespiratory disease	78 (38)	132 (36)
Site of tumour		
Caecum	25 (12)	36 (10)
Ascending colon	14 (7)	17 (5)
Hepatic flexure	8 (4)	8 (2)
Transverse colon	16 (8)	22 (6)
Splenic flexure	24 (12)	9 (2)
Descending colon	15 (7)	13 (4)
Sigmoid colon	57 (28)	97 (27)
Rectum	46 (22)	158 (44)
Tumour spread		
None	78 (38)	177 (49)
Local	66 (32)	79 (22)
Distant	21 (10)	26 (7)
Local and distant	32 (15)	72 (20)
Unknown	10 (5)	9 (2)
Dukes' classification		
A	2 (1)	16 (4)
B	54 (26)	117 (32)
C	57 (28)	103 (28)
Distant metastases	64 (31)	107 (29)
Unknown	30 (15)	20 (6)
Grade of operating surgeon		
Consultant	102 (49)	229 (63)
Non-consultant	82 (40)	88 (24)
No operation	18 (9)	13 (4)
Not recorded	5 (2)	33 (9)

Values in parentheses are percentages

Table 2 Surgical procedures for patients undergoing emergency or elective colorectal surgery

	Emergency surgery	Elective surgery
Curative resection	94 (45)	212 (58)
Palliative resection	38 (18)	66 (18)
Palliative diversion	49 (24)	66 (18)
Laparotomy only	8 (4)	6 (2)
No operation	18 (9)	13 (4)

Values in parentheses are percentages

Table 3 Resection rates by age group for patients undergoing emergency or elective colorectal surgery

Age (years)	Emergency surgery	Elective surgery
< 55	30 (75)	55 (81)
55-64	31 (76)	84 (79)
65-74	40 (61)	98 (77)
≥ 75	31 (52)	41 (66)

Values in parentheses are percentages

a resection which was considered to be curative. Resection rates were higher in elective situations for patients with local spread (63 *versus* 48 per cent), distant spread (69 *versus* 48 per cent) or both (46 *versus* 38 per cent).

Operative mortality

Thirty-one patients did not undergo surgery (Table 2). The 30-day operative mortality rate was higher in the emergency

group than in the electively treated group (19 *versus* 9 per cent, $P < 0.001$; Table 5). The operative mortality rate was similar in the two groups for young patients but much greater in the emergency group for patients older than 65 years (24 *versus* 8 per cent).

The operative mortality rate was lower in the elective situation whether the primary tumour was situated in the right colon (13 *versus* 21 per cent), left colon (7 *versus* 18 per cent) or rectum (9 *versus* 13 per cent).

Following tumour resection the mortality rate was similar, and relatively low, in both groups: 7 per cent in the elective group and 8 per cent in the emergency group (Table 5). The mortality rate was much greater in the emergency group for patients undergoing palliative diversion (39 *versus* 15 per cent) or laparotomy alone (62 *versus* 17 per cent).

For patients older than 65 years, the operative mortality rate following resection was relatively low in both groups: 12 patients (9 per cent) died in the elective group and nine (13 per cent) in the emergency group. For those older than 65 years undergoing palliative diversion or laparotomy alone, 18 patients (45 per cent) died in the emergency group compared with three (7 per cent) in the elective group.

Operative mortality rates for primary and secondary emergency resection are shown in Table 6.

Survival

The 5-year survival rate (disease-related mortality rate) was greater for those presenting electively whether postoperative deaths were included (33 *versus* 16 per cent) or excluded (37 *versus* 19 per cent, $P < 0.001$; Figure 1). The higher 5-year

Table 4 Relationship between extent of disease and treatment

	Emergency surgery	Elective surgery
No spread		
Curative resection	78 (100)	177 (100)
Local spread		
Curative resection	16 (24)	35 (44)
Palliative resection	16 (24)	15 (19)
Palliative diversion	32 (48)	29 (37)
Laparotomy only	2 (3)	0 (0)
Distant spread		
Palliative resection	10 (48)	18 (69)
Palliative diversion	6 (29)	5 (19)
Laparotomy only	2 (10)	2 (8)
No operation	3 (14)	1 (4)
Local and distant spread		
Palliative resection	12 (38)	33 (46)
Palliative diversion	11 (34)	32 (44)
Laparotomy only	3 (9)	3 (4)
No operation	6 (19)	4 (6)

Values in parentheses are percentages

Table 5 Operative mortality

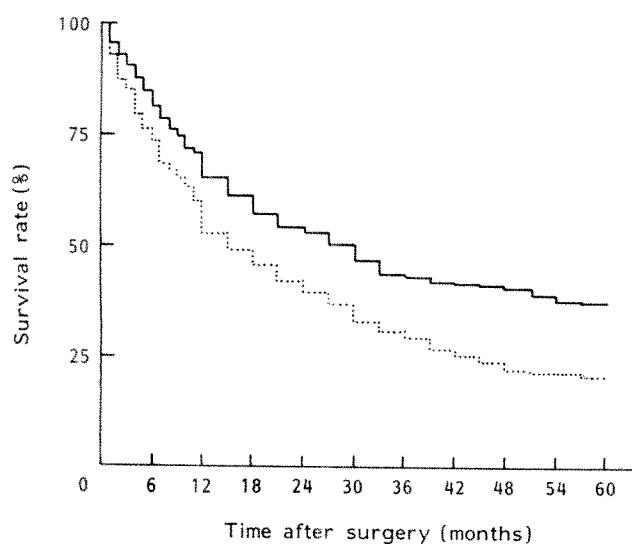
	Emergency surgery	Elective surgery
Age (years)		
< 55	3 (8)	4 (6)
55-64	5 (12)	12 (11)
65-74	12 (21)	8 (7)
≥ 75	15 (28)	7 (12)
Type of surgery		
Curative resection	6 (6)	11 (5)
Palliative resection	5 (13)	9 (14)
Palliative diversion	19 (39)	10 (15)
Laparotomy only	5 (62)	1 (17)
Total	35 (19)	31 (9)

Values in parentheses are percentages

Table 6 Outcome of emergency surgery

	Total patients	30-day mortality	5-year survival*
Primary resection	90	8 (9)	23 (29)
Defunction then secondary resection	28	0 (0)	4 (29)
Hartmann's procedure	8	2 (25)	1 (33)
Bypass/laparotomy only/no surgery	81	40 (49)	0 (0)

Values in parentheses are percentages. *Disease-related percentages based on life-table estimation

**Figure 1** Survival curves for patients with colorectal cancer treated electively (—) or as an emergency (.....)**Table 7** Disease-related survival, excluding operative mortality

	Emergency surgery	Elective surgery
5-year survival rate		
Age (years)		
<55	24	40
55-64	26	39
65-74	20	39
≥75	16	29
Tumour spread		
None	36	64
Dukes' classification		
A	50	77
B	31	67
C	27	33
Total	19	37
Other survival data		
2-year survival rate with local tumour spread	10	14
Median survival time (days)		
Distant tumour spread	265	367
Local and distant tumour spread	164	187

Values for survival rates are percentages

survival rate in elective patients was evident for all age groups, Dukes' classes and degrees of spread (Table 7). None of the three emergency patients with perforation, 17 per cent of those with obstruction, 31 per cent of those with haemorrhage and 20 per cent of those with neither perforation, obstruction nor haemorrhage survived for 5 years.

Survival rates following primary and secondary emergency resection are shown in Table 6.

Table 8 Relative hazard ratios for adjusted survival of all patients treated (postoperative deaths omitted)

	Relative hazard ratio	95 per cent confidence interval	P
All patients*	1.34	1.07-1.69	<0.05
Curative resections†	1.57	1.11-2.23	<0.01
Palliative resections‡	0.78	0.49-1.23	n.s.
Palliative diversions‡	1.38	0.87-2.19	n.s.

*Adjusted for spread, stage and resection rate; †adjusted for age, spread and stage; ‡adjusted for presence of distant spread; n.s., not significant

Multivariate analysis

Significant factors determining operative mortality were age, emergency admission and pre-existing cardiorespiratory disease. Logistic regression analysis confirmed a higher operative mortality rate in the emergency cohort when the data were corrected for age and pre-existing cardiorespiratory disease ($P < 0.01$).

The 5-year survival rate was higher ($P < 0.05$) for electively admitted patients even when corrected for the predictive factors of disease stage, degree of spread and type of surgery (Table 8). Five-year survival following curative resection was higher in patients treated electively when the data were corrected for age, disease spread and disease stage ($P < 0.01$).

Discussion

It is recognized that patients with colorectal cancer who present as an emergency are less likely than their electively treated counterparts to have their tumour resected⁵. Whether this difference reflects resectability *per se* is debatable. The difference in resectability between emergency and elective groups in the present study appears to apply to the curative (45 versus 58 per cent) rather than the palliative (18 per cent for both groups) resection rates (Table 2). This may have been because emergency patients underwent palliative rather than curative resections. Of those patients who were thought to have only local tumour spread, 24 per cent of emergency patients underwent an apparently curative resection compared with 44 per cent of elective patients (Table 4) and patients with evidence of distant spread were more likely to have their tumour resected if they presented electively (52 versus 42 per cent). It appears, therefore, that resection rates may have been influenced by more aggressive and optimistic management in the elective situation. This may reflect the surgeon's perception of the extent of disease or ability to undertake resection.

Increased mortality rates following emergency colorectal cancer surgery have been attributed to a higher incidence of infection, anastomotic leakage and bronchopneumonia³. Elderly patients have a higher perioperative mortality rate¹². There was a slight excess of patients older than 65 years undergoing emergency surgery in this study, which may partially account for the increased mortality rate. Logistic regression analysis demonstrated that factors other than age and pre-existing cardiorespiratory disease also influenced operative mortality.

Patients with obstruction, perforation or haemorrhage might present more frequently in the emergency group and have a particularly poor outcome. Those without these complications in the emergency cohort, however, still have a worse prognosis in terms of 30-day mortality rate (28 versus 9 per cent) and 5-year survival rate (20 versus 33 per cent).

Mortality rates following tumour resection were similar, and relatively low, in both groups, although for those undergoing palliative diversion or exploratory laparotomy, the mortality rate was much greater in the emergency group. Other potential causes of high mortality in the emergency cohort include insufficient preoperative resuscitation and inadequate surgical technique.

Survival is worse in patients undergoing emergency surgery

than in those receiving elective treatment^{4,5}. In this series the 5-year survival rate was better in the elective situation regardless of age, disease stage or degree of tumour spread. Patients presenting as emergencies with intestinal obstruction had a higher resection rate and lower operative mortality rate but 5-year survival was considerably better when patients with these symptoms presented electively. This difference cannot be explained by the excess of patients in the emergency cohort presenting with obstruction, perforation or haemorrhage because those without these complications had a better survival rate if treated electively. When disease-related survival was assessed and operative mortality excluded, the 5-year survival rate following an apparently curative resection for patients with no evidence of spread was almost twice as high in the elective group. A preliminary defunction did not improve the survival of emergency patients compared with those undergoing primary resection (Table 6). Underestimation of the extent of tumour spread at the time of primary surgery results in an insufficiently extensive resection and leads to increased recurrence¹³; differences in survival between groups may reflect suboptimal surgical technique in the emergency situation.

This prospective study confirms that the outcome following emergency colorectal cancer surgery is significantly inferior to that after elective surgery. Some patients may receive suboptimal surgery in the emergency situation. Earlier diagnosis of colorectal cancer may reduce the incidence of emergency presentations, especially in elderly patients.

Acknowledgements

This study was made possible by the foresight of Professor L. H. Blumgart and Mr C. B. Wood who established the colorectal cancer follow-up clinic in 1974. The authors are grateful to the Cancer Research Campaign for financial assistance.

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Paper accepted 5 February 1992

Erratum

Ljungman C, Adami H-O, Bergqvist D, Berglund A, Persson I. Time trends in incidence rates of acute, non-traumatic extremity ischaemia: a population-based study during a 19-year period. *Br J Surg* 1991; **78**: 857–60.

An error by the authors unfortunately led to Figures 2 and 4 of the above paper overestimating incidence rates by a factor of ten. The correct y axis for Figure 2 should indicate an incidence ranging from 0 to 40 per 100 000 and that in Figure 4 from 0 to 10 per 100 000.

While the absolute values published are incorrect, the time trends of the incidence rates for arterial occlusion reported and the conclusions drawn remain valid. The authors apologize to the reader for any confusion caused.

Conservative management of asymptomatic popliteal aneurysm

Sir

It is well known that whichever treatment policy is instituted, acute thrombosis of a popliteal aneurysm often results in amputation. It has been suggested¹ that the treatment of choice in this situation may be low-dose intra-arterial thrombolysis followed by reconstruction once patency has been achieved. While this policy has many attractions, we would like to draw readers' attention to a possible hazard.

Our patient was a 48-year-old schoolteacher suffering from hyperlipidaemia who was admitted with an acutely thrombosed popliteal aneurysm of the right leg. Symptoms consisted of sudden onset, severe claudication with mild rest pain associated with coolness and pallor of the lower leg and foot. On examination, it was noted that movement and sensation in the leg were normal and the calf muscles soft and non-tender. All pulses distal to the femoral pulses were absent in that leg. In view of the critical nature of the ischaemia, low-dose intra-arterial streptokinase was instituted. Initially, progress was satisfactory with the aneurysm becoming pulsatile within a few hours and a clinical improvement in the perfusion of the upper calf. There was filling of a posterior tibial artery in the mid and lower calf on the 12-h angiogram. However, by 18 h the arteriogram showed no calf or distal vessel filling and this was followed by an acute deterioration in the foot itself. Despite further catheter advancement and continual infusion of streptokinase, the bulk of the foot did not recover and below-knee amputation was carried out 2 weeks later. It was planned to operate on a contralateral popliteal aneurysm as an urgent/elective procedure, but 2 weeks after discharge the patient was readmitted with an acute thrombosis of this aneurysm. Although critical, the ischaemia was not immediately limb-threatening and therefore intra-arterial thrombolysis was again instituted but this time using tissue-activated thrombolytic. Once more, the signs of revascularization of the aneurysm, together with an initial improvement of the proximal calf, were quickly followed by more severe, distal ischaemia of the foot and calf muscles. At emergency operation, the small vessels of the calf and foot were found to be occluded by a mixture of organizing thrombus and atheroma which proved refractory to femorodistal grafting.

We have no evidence in this case that emergency reconstruction on its own would have achieved a more successful outcome and, indeed, the data presented by the Guildford group are persuasive that a conservative policy would be successful in most cases. It is our impression in this case, however, that thrombolysis of the popliteal thrombus resulted in distal embolization to such a degree that successful distal reconstruction was compromised. We would like to sound a warning on the use of thrombolysis in this situation and would be interested to hear if others have experienced similar problems.

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Retrograde femoral angioplasty: a new technique

Sir

Mr Shanahan and colleagues (*Br J Surg* 1991; 78: 1134-5) claim to introduce retrograde femoral angioplasty as a new and previously unpublished technique. Retrograde femoral angioplasty, however, was first reported¹ in 1988. In this paper, documenting 50 patients, access to the superficial femoral artery was achieved by percutaneous puncture of the popliteal artery, in contrast to the surgical exposure of the popliteal artery as currently described. Percutaneous retrograde femoral angioplasty is now practised by many experienced interventional vascular radiologists. This percutaneous technique is relatively simple and initially involves percutaneous insertion of a 4- or 5-Fr

catheter into the ipsilateral common femoral artery. After turning the patient prone and injecting angiographic contrast media via the proximally placed catheter, the popliteal artery is catheterized under direct fluoroscopy. Puncture is facilitated by road-mapping angiographic techniques, but these are by no means essential. Percutaneous puncture of the popliteal artery clearly has many advantages over surgical exposure. There is also no evidence that it is associated with a higher complication rate compared with common femoral artery puncture.

The authors fail to provide important technical details such as the number of patients with stenoses versus occlusions, the lengths of occlusions treated, the size of balloons used, balloon inflation times, and whether anticoagulation was employed. In four of the six patients reported, an occlusion could not be crossed by a guidewire and a laser was used to attempt recanalization. This is a high technical failure rate, and it is not clear whether the newer hydrophilic guidewires were used in addition to conventional guidewires before resorting to the laser, particularly relevant in view of its high perforation rate. Before dilatation, it is important that the balloon catheter is known to be in an intraluminal position. This precaution avoids the risk of occluding the profunda femoris artery origin that may result from dilatation in a subintimal position. This important technical point was not addressed.

The indication for retrograde superficial angioplasty, as compared to the conventional antegrade approach, is not solely a lesion of the origin of the superficial femoral artery. Indications also include patients with lesions in the mid and distal superficial femoral artery, in whom passage of a guidewire has been unsuccessful, or is unlikely to succeed because of collateral anatomy, and some obese patients where antegrade puncture of the common femoral artery is not practical. In this last group, however, retrograde common femoral artery puncture is usually possible, allowing successful retrograde popliteal artery puncture and angioplasty.

Finally, of related interest, retrograde profunda femoral angioplasty for profunda femoris origin stenosis has also been described².

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Staple-line erosion: a common source of recurrent bleeding following stapled oesophageal transection

Sir

We read with interest the recent article by Kaye *et al.* (*Br J Surg* 1991; 78: 1355-7) on bleeding from a staple-line erosion after stapled oesophageal transection. Recently we made a similar observation on a patient with an oesophagojejunal anastomosis following a total gastrectomy for gastric cancer. A Braun loop had been employed. Seven days later the patient developed upper gastrointestinal bleeding and the haemoglobin level dropped to 3 g/dl. At endoscopy there was no oesophagitis, only bleeding from an erosion above the protruding mass of the staple line. After two sclerotherapy sessions the bleeding was controlled.

Although it is stated that staple-line erosions are associated with acid reflux, that can hardly have been the case in this patient who had undergone total gastrectomy. Perhaps protrusion of the staples is

acid suppression therapy will not be beneficial. Endotherapy should be used to control the bleeding.

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Therapeutic aspects of radioisotopes in hepatobiliary malignancy

Sir

We enjoyed reading the Review by Novell *et al.* (*Br J Surg* 1991; 78: 901-6).

We agree with most of the points raised, but differ from the authors in the opinion that iodine-131 is a better radioisotope to use when compared with yttrium-90. We feel that this issue is still unsettled.

The authors emphasized two major side-effects of yttrium-90, namely leaching of yttrium-90 from the resin or ceramic matrix with accumulation of the isotope in bone leading to bone marrow suppression, and the embolic effects of the infusing microspheres resulting in shunting of the spheres to the lungs and other organs and leading to pulmonary fibrosis and gastrointestinal bleeding. Improvements in radiopharmaceutical techniques have resulted in much safer yttrium-90 microspheres and their system of delivery¹⁻⁴. A routine leach test on the yttrium-90 microspheres (supplied by the Australian Nuclear Science and Technology Organisation) before treatment of our patients showed that the leaching was always <1 per cent. The use of technetium-99m-radiolabelled macroaggregate albumin in the pretreatment assessment of potential shunts and tumour:normal dose ratio helps us in better patient selection. The use of an intraoperative β -probe to scan and assess the radiation dosage to the tumour, normal liver tissue and other intra-abdominal organs further enhances the safety of the yttrium-90 microspheres. In our hands, such microspheres are very safe to use.

There are many advantages of yttrium-90 over iodine-131. Yttrium-90 has a large field of irradiation, it has a longer cytotoxic range and a greater tumour dose rate, and therefore it can be used in larger and relatively less vascular lesions. Isolation of the patient is not required because it is a pure β -emitter. It is not biodegradable and no radioactive product enters the systemic circulation if the percentage of leach is zero. It has, however, the disadvantage of difficulty in determining the dosimetry. If required, dosimetry has to be undertaken during operation with β -probing. Moreover, its uptake in therapeutic amounts by multiple small deposits may result in the delivery of an unacceptable radiation dose to the surrounding normal tissue.

On the other hand, iodine-131 has an advantage over yttrium-90 in that dosimetry can be done with γ -scintigraphy without an operation. This makes pretreatment assessment, fractionation and repeated treatment under monitoring with dosimetry possible. Furthermore, the tumour:normal dose ratio is enhanced by a differential uptake and a differential half-life of Lipiodol-iodine-131 in the tumour and in the normal tissue. This is in addition to the effects of vascularity and the instantaneous arterial blood flow to the tumour (improved with the use of vasoactive agents), which are the only factors that determine the tumour:normal dose ratio in yttrium-90 microspheres. As mentioned previously, iodine-131 has the disadvantages of smaller field of irradiation, shorter cytotoxic range and a lesser tumour dose rate and it is, therefore, less suitable for large tumours. Radiation protection is necessary because of its γ -radiation. Also, radioactive degradation products can enter the systemic circulation and be excreted, and blockage of the thyroid gland with potassium iodide and disposal of radioactive urine are additional safety measures that need to be undertaken.

It appears that both yttrium-90 and iodine-131 have relative advantages and disadvantages. At present, we are in the process of determining which is the better isotope in the treatment of patients with primary or secondary liver cancer. We hope to obtain an answer in the near future.

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Surgical management of the thoracic outlet compression syndrome

Sir

We read with interest the article by Davies *et al.* (*Br J Surg* 1991; 78: 1193-5). This series has again demonstrated that well selected patients derive considerable benefit from decompression of the thoracic outlet. We would, however, disagree with the principal conclusion of the article: that vascular symptoms are adequately treated by excision of the cervical rib alone. This is contrary to our impressions and the experiences of others¹. The basis of this assertion is the good result in all 15 patients following excision of a cervical rib alone, compared with improvement in 18 of 20 after excision of a first rib. As the authors stress, the difference is not significant and may in fact reside in the two patients who required arterial thrombectomy, which is associated with a poorer result². Second, two patients who had persistent symptoms after excision of their cervical ribs alone elsewhere gained relief from excision of the first rib.

To concentrate on a cervical rib in these patients may encourage a reversion to the attitude that symptoms do not occur in the absence of an abnormal rib, and so deny many patients appropriate therapy.

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Colectomy with ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis

Sir

I feel I must take issue with the conclusions drawn by Madden *et al.* (*Br J Surg* 1991; 78: 789-92) on the suggested operative strategy in patients with familial polyposis. The authors advocate colectomy with ileorectal anastomosis (IRA) rather than restorative proctocolectomy (RPC) as the procedure of choice in the majority of patients. This conclusion is based on the shorter postoperative stay, lower complication rate and better functional result after IRA. The comparison, as outlined in the study is, I feel, open to criticism.

One concern is that the study compares an operation (RPC) that eradicates the risk of the subsequent development of rectal carcinoma with one (colectomy and IRA) that does not. Perhaps a fairer comparison would have been between RPC and panproctocolectomy with permanent ileostomy. A further major concern is that of 82 patients who underwent IRA, almost a quarter (24 per cent) were not included in the analysis. Six patients died, from unspecified causes, and 14 were lost to follow-up.

The authors play down the importance of the risk of development of cancer in the rectal stump after IRA. They do, however, admit that even with meticulous 6-monthly examination over the study period, almost one patient in ten could be expected to develop a rectal cancer.

A previous report from St Mark's Hospital¹ has demonstrated that most of these tumours are advanced at presentation (Dukes' B and C lesions). Data from The Mayo Clinic experience² would suggest a much higher incidence of stump carcinoma, in the region of 59 per cent at 23 years. These data are supported by a further study from West Virginia³, where an incidence of 22 per cent was reported after a mean follow-up of only 14 years. The majority of patients undergoing surgery for polyposis was young; it is not unusual, therefore, for these patients to survive for at least 20 years. This high incidence of rectal carcinoma after long-term follow-up is of concern.

The data on postoperative stay, complications and function contain bias. The study period started in 1977 when RPC was in a developmental stage. Conversely, colectomy with IRA was a well established procedure. The authors admit that postoperative stay has significantly decreased after RPC in the latter half of the study. Furthermore, the complication rates and functional results have also improved with time. It would therefore be of interest to know the complication rate and functional results of RPC compared with IRA in the latter half of the study period.

There is little doubt that patients spend longer in hospital after RPC. The study, however, is biased in including patients who underwent RPC as a secondary procedure. This group have already undergone one major abdominal operation and presumably, if the postoperative stay after the initial IRA is added to that after secondary RPC, these patients spend far longer in hospital overall. Added to this are the 3 days that many of them spent in hospital every 6 months during the period that their rectal stump was under surveillance.

Most complications after RPC were related to the stoma. Many centres are now performing RPC without a stoma in selected cases. Again, the inclusion of patients having RPC as a secondary procedure biases the comparison. Most patients who developed intestinal obstruction were those having a secondary procedure. A high incidence of intestinal obstruction could be expected in this group, as they have already undergone one major laparotomy. If this group of patients is excluded from the analysis, there is no significant difference in the incidence of postoperative intestinal obstruction between RPC as a primary procedure and IRA. Apart from intestinal obstruction, postoperative complications appear significantly greater following RPC but it must be asked how many of these occurred in the early, development stage of the procedure.

With regard to postoperative function, the only significant differences were an increased bowel frequency and nocturnal evacuation after RPC. The ability to defer defaecation was worse after IRA. The data on sexual activity are unclear while those on time to resumption of normal activity may be related to the early technical problems with RPC.

Overall, I do not feel a strong enough case has been made for colectomy and IRA as a procedure of choice in familial polyposis. The impetus for IRA as an alternative to panproctocolectomy came from a desire to avoid a permanent stoma and improve quality of life. RPC fulfils these criteria, but importantly it also eliminates the risk of subsequent development of a rectal carcinoma.

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Glutamine-enhanced enteral diet improves nitrogen balance without increasing portal ammonia

Sir

It is sad to see perpetuation in the paper by Brown *et al.* (*Br J Surg* 1991; **78**: 1305-6) of the myth that following surgical trauma there will be a period of negative nitrogen balance and that 'without vigorous nutritional support, such a patient will become rapidly protein depleted,

which may lead to an increased risk of death'. It is inappropriate to group together or severe metabolic illness, and there is no evidence in the literature to suggest that a short period of endogenous metabolism after surgery is harmful to individual patients. Equally there is no evidence supporting nutritional therapy for these patients.

Another major criticism of this paper is its use of nitrogen balance as the main criterion of benefit. It is true that nitrogen balance was a parameter widely used in metabolic studies a decade or so ago, but it is unfortunate to see this criterion alone being used in 1991.

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Suture length to wound length ratio and the integrity of midline and paramedian incisions

Sir

I read with interest the article by Kendall *et al.* (*Br J Surg* 1991; **78**: 705-7) which recommended the lateral paramedian incision as superior to the midline incision closed with the mass technique. Although their total absence of complications with this incision was impressive, there are some serious biases in the randomization, each of which may not be statistically significant but summated would weigh heavily against midline mass closure.

	Incision	
	Lateral paramedian	Midline mass
Registrar	50	58
Malignancy	30	53
Emergency	19	31
Operation		
Large bowel	32	48
Upper gastrointestinal	54	40
Infection	7	11

Values are percentages

One wonders how 30 more patients were randomly allocated to lateral paramedian incision than either of the midline techniques. I would suggest that without more stringent randomization the case against midline mass closure with a suture:wound length ratio of greater than 4:1 is still unproven.

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Rebound tenderness test

Sir

I write with regard to the paper by Messrs Liddington and Thomson (*Br J Surg* 1991; **78**: 795-6) on the limited value of rebound tenderness as a predictor of peritonitis and the subsequent (conflicting) correspondence on this matter from Professor Irving (*Br J Surg* 1991; **78**: 1510), Mr Anderson (*Br J Surg* 1991; **79**: 184), Mr Dixon and colleagues (*Br J Surg* 1992; **79**: 280-1), and Messrs Hashimi and Stewart (*Br J Surg* 1992; **79**: 281). Perhaps the last word should belong to the late Sir Wilfred Trotter¹.

'When you ask a patient if you are hurting him, nine times out of ten he will respond with touching cheerfulness, "Not yet, Doctor". What a succession of iron thumbs is disclosed by that answer! Some ... have thought that the man who has the handling of sick human bodies should make himself ambidextrous. I do not subscribe to that, but I sometimes think that

responsible, in which case well to limit himself to the possession of and sclerotherapy should be used.

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This is indeed the last word – Editor.

Cholecystectomy and gallbladder conservation

Sir

I read with interest the Leading Article by Walsh and Russell (*Br J Surg* 1992; 79: 4–5). The numerous problems that arise after cholecystectomy in about half the patients who have their gallbladder removed have been stated by the authors, who rightly suggest that in many situations conservation of the gallbladder is desirable.

It seems reasonable to assume that laparoscopic cholecystectomy will represent the standard operative technique for removal of the gallbladder. However, Walsh and Russell suggest that laparoscopic cholecystectomy is likely to reduce the impetus to further research into procedures that conserve the gallbladder. Evidence is emerging from various workers, including Cuschieri and Berci¹, Perissat *et al.*^{2,3} and Morris and colleagues⁴, that laparoscopic cholecystectomy is a good operative measure for removing gallstones without removal of the gallbladder. The only criterion is a contractile gallbladder: the chemical composition of the gallstones is unimportant. The gallbladder is incised and stones are removed via the laparoscope. The incision within the gallbladder is closed by suture clips. The technique itself is minimally invasive and allows the removal of the stones within 40–60 min. It would be of great value and interest to gastroenterologists, endoscopists and surgeons if prospective studies were to be undertaken in future between laparoscopic cholecystectomy and laparoscopic cholecystotomy. Only such studies would clearly define whether or not there is benefit from conservation of the gallbladder in the treatment of gallstone disease.

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A laparoscopic hazard for the surgeon

Sir

The rapid, widespread introduction of laparoscopic surgery has resulted in many benefits for patients. However, there is little doubt that this technology has been implicated in the aetiology of many injuries¹. Early data suggest that some of these injuries are inherent to the technique and the constraints it places on the surgeon. We have recently observed a complication that is another manifestation of the risks of laparoscopic procedures.

One of us assisted the other in performing a laparoscopic abdominoperineal resection of the rectum and as such held a laparoscopic bowel clamp in a fixed position for approximately 2 h 30 min. The morning after the operation, the surgeon experienced severe pain on the medial aspect of the left arm radiating down into the ulnar

border of the hand. The pain could be recreated by pressure in the axilla and a diagnosis of pectoralis major tendonitis was reached. This was treated by oral non-steroidal anti-inflammatory drugs and rest.

Morbidity among surgeons as a result of their profession has previously been reported. At University College Hospital, London, the first Professor of Surgery, Robert Liston, performed a procedure with a 300 per cent mortality rate. During a leg amputation, he also excised his assistant's fingers and tore a spectator's coat. The former died from gangrene (as did the patient), the latter of fright². Semmelweis and Pfannenstiel also both succumbed to hand infections sustained during their professional activities³. Brenkel *et al.* reported a third metacarpal fracture sustained by an orthopaedic surgeon while attempting to reduce a Thompson's prosthesis into the acetabulum⁴.

Overuse of muscle groups can lead to a variety of afflictions known variously as tenosynovitis, repetitive strain injury or cumulative trauma disorder⁵, and such afflictions are not uncommon among surgeons. These overuse syndromes have been described in breast augmentors⁶ and anaesthetists who use an extended thumb to keep a face mask in position⁷. Acute carpal tunnel syndrome has been reported in a surgeon who used his non-dominant hand to retract the bowel during a lengthy biliary procedure⁸. However, not only does overuse lead to morbidity among physicians, quite the opposite may be the case. In one instance, a neurosurgical assistant attempted to sit on an adjustable stool as the seat became disconnected. The shaft of the stool entered his anus and the injury that resulted necessitated a defunctioning colostomy⁹.

The case presented represents an additional hazard of laparoscopic surgery and may prompt the development of more pliant and less easily traumatized mechanical systems to provide retraction.

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Adjuvant herbal treatment for gallstones

Sir

I was amused to read the recent Case Report on herbal treatment for gallstones by Savage *et al.* (*Br J Surg* 1992; 79: 168).

A patient of mine, a man approaching 60 years of age, was known to have multiple stones in the gallbladder on ultrasonography, but had no clinical, biochemical or ultrasonographic evidence of common bile duct stones. He presented 2 weeks before cholecystectomy bearing a pickle jar about one-third full of what appeared to be numerous light-green gallstones. He somewhat shamefacedly told me that he had succumbed to the advice of a friend to take 1 pint of olive oil with lemon juice over a short period of time, which he had been told would cure his gallstones. He reported passing about six stones the size of a broad bean and numerous others the size of a pea. He described the stones as being quite soft, although regrettably I failed either to feel one for myself or to have one analysed.

In spite of this apparent success of the olive oil treatment I still found the whole episode difficult to believe. Repeat ultrasonography and oral cholecystography confirmed the presence of a gallbladder packed with stones of different sizes. At operation as planned 2 weeks later a gallbladder full of stones was uneventfully removed. The cystic

duct was only just big enough to admit the cholangiogram catheter and peroperative cholangiography showed an entirely normal biliary system.

To quote W. S. Gilbert (*HMS Pinafore* Act II): 'Things are seldom what they seem – skim milk masquerades as cream.' In this case I am certain that the curious faecal pellets resulted from the massive olive oil intake and were masquerading as gallstones. I have yet to persuade any of my medical students to try this herbal remedy in the cause of science.

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Pancreas and islet transplantation

Sir

I read the recent Leading Article on pancreas and islet transplantation by London and Bell (*Br J Surg* 1992; **79**: 6–7) with great interest and should like to make the following comments.

1. The significantly reduced graft survival in vascularized pancreas transplants alone, compared with synchronous vascularized pancreas–kidney transplants from the same donor, cannot be ascribed to technical problems. In the combined operation, plasma creatinine acts as an early and sensitive indicator of rejection and its response to treatment¹. This surrogate marker of pancreatic rejection is absent in pancreas transplantation alone. Instead the diagnosis of rejection in these patients is dependent on a fall in urinary amylase². However, urinary amylase levels can be unreliable as they are affected by daily fluctuations in the urine output and pancreatic exocrine secretions. The increased graft loss in pancreas transplantation alone, therefore, reflects the difficulties and delays in diagnosing rejection. The value of serum immunoreactive anodal trypsinogen as a consistent indicator of early pancreatic rejection, if confirmed, would be a major contribution to the management of patients undergoing pancreas transplantation³.

2. The only proven benefit of combined vascularized pancreas–kidney transplants is an improvement in the quality of life of the recipients⁴. Recurrent diabetic nephropathy in patients with type 1 diabetes mellitus is a rare cause of graft loss, and its prevention should not be regarded as an indication for pancreatic transplantation⁵.

3. It is incorrect to state that 'the purification of large numbers of viable, sterile islets' has been achieved in humans. The yield of islets from a single adult human pancreas has indeed been improved by the techniques developed by the St Louis and Leicester groups^{6,7}. Nevertheless, this is still insufficient for clinical transplantation purposes and pooling from more than one donor pancreas is necessary. Furthermore, similar to previous islet preparations, the final isolates obtained by current techniques are contaminated with exocrine, lymphoid and vascular tissue⁶. What has altered is the fact that purity is no longer regarded as a prerequisite for islet transplantation.

4. While there is no doubt that islet transplantation is a technically simpler procedure, it is important to emphasize that a successful vascularized pancreas graft is the only available means of achieving long-term normal glucose metabolism in humans⁸. There are no animal or human experimental data to show that islet transplantation can be equally effective. These disappointingly poor results cannot simply be equated with the use of suboptimal numbers of islets. Despite the implantation of adequate numbers of islets and the initial restoration of normoglycaemia, unexplained graft loss is common at a later stage in islet autotransplantation and syngeneic transplants^{9,10}. Thus, islet transplantation cannot at present be considered as an alternative to vascularized pancreas grafts.

5. If islet transplantation is to have a wider clinical application, life-long immunosuppression of the recipient must be avoided. Islets are more immunogenic than vascularized pancreas grafts¹¹. Theoretically, the depletion or destruction of interstitial class II⁺ dendritic cells – believed to be responsible for triggering the rejection process – would render islets non-immunogenic and obviate the need for postoperative immunosuppression. Tissue culture is the most commonly used method of islet immunomodulation. Although its value in humans remains to be proven, a major advantage of free graft incubation is that it is considered to be safe. However, in the case of the human fetal pancreas, it has recently been reported that this assumption might not be correct¹². The expression of the major histocompatibility complex class I and II antigens by parenchymal cells of the human fetal pancreas in response to interferon- γ is markedly enhanced following conventional tissue culture (incubation in 5 per cent carbon dioxide in humidified air at 37°C) using RPMI 1640 medium. In addition, the loss of dendritic

cells in the cultured pancreases was incomplete in all cases. In effect, tissue culture before transplantation might increase, rather than reduce, allograft susceptibility to immune destruction. It is not known whether the adult human pancreas is subject to the same influences, but its immunomodulation by tissue culture certainly needs closer scrutiny in the light of these findings.

Investigators involved in pancreas and islet transplantation are aware of the enormous hurdles that lie ahead. The implementation of the clinical islet transplantation programme at Leicester is a welcome filip to us all.

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Authors' reply

Sir

We are grateful for the interest Mr Koo Seen Lin has shown in our Leading Article. The article was of necessity brief and so, therefore, will be our response.

1. We did not state that the reduced graft survival in vascularized pancreas transplants alone compared with synchronous vascularized pancreas–kidney transplants is related to technical problems, and we of course agree that the major problem with pancreas transplantation alone is the early detection of rejection.

2. We clearly stated that the most definite benefit from the addition of a pancreas to a kidney transplant is an improved quality of life.

3. Those of us actively involved in the field of human islet transplantation consider preparations of high purity a prerequisite for success. Indeed, one of the major differences between recent and previous series of islet transplants has been their greatly improved purity. We entirely disagree, therefore, that purity is no longer regarded as a prerequisite for islet transplantation, indeed much of the effort and research time of those actively involved in this field has been directed towards this very purpose. It is now possible to purify large

from a single human pancreas and it would seem that the major problem facing islet transplantation at the moment is not transplanting sufficient islets, but preventing those islets that have been transplanted from being rejected.

4. The article made clear that at the present time islet transplantation is not routinely successful.

5. There is no evidence whatsoever that human islets are more immunogenic than vascularized pancreas grafts, although on the basis of the available data it would be reasonable to conclude that they are equally immunogenic. The paper that Mr Koo Seen Lin quotes was a mental study in rats. We agree with him that the concept of immunomodulation being concerned purely with the functional deletion of antigen-presenting cells is outdated; indeed we have recently shown¹ that tissue-cultured human islets and exocrine tissue express major histocompatibility complex (MHC) class I and II antigens. Mr Koo Seen Lin's work on cultured human fetal pancreas tissue is fascinating, but he should be careful not to extrapolate results with fetal pancreas tissue cultured in the presence of interferon- γ to the situation with human islets cultured in the absence of such substances that are known to enhance MHC expression.

We agree with Mr Koo Seen Lin that investigators involved in islet transplantation are aware of the challenges that lie ahead. If advances in the field continue at their present rate, then providing that these hurdles are approached in a scientific and rational manner, there is every reason to think that the finishing tape is in sight.

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Flushing technique in the management of retained common bile duct stones with a T tube *in situ*

Sir

We read with great interest the article by Soravia *et al.* describing a flushing technique for the management of retained common bile duct (CBD) stones (*Br J Surg* 1992; 79: 149–51). Of interest is the observation that five of 40 retained stones (12 per cent) passed spontaneously into the duodenum. In a recent series in the USA of 126 postoperative T tube tract choledochoscopies for retained biliary calculi, 21 patients (16.7 per cent) had a normal choledochoscopic examination and needed no further treatment¹. These studies confirm the previous observation that spontaneous passage of retained CBD stones is not unusual² and suggest that the initial management of retained stones should be simple observation.

Controversy currently exists as to the correct approach to unsuspected CBD stones during laparoscopic cholecystectomy^{3,4}. Over a 20-month period we attempted 300 consecutive laparoscopic cholecystectomies, with a conversion rate of 9 per cent. Selective preoperative or peroperative cholangiography was positive in seven of 32 patients (22 per cent) with historical, clinical or biochemical evidence of choledocholithiasis. Of 240 patients who underwent laparoscopic cholecystectomy without cholangiography, three (1.2 per cent) subsequently re-presented with symptoms referable to CBD stones and only two of them proved to have biliary calculi at endoscopic retrograde cholangiopancreatography. We suggest that selective cholangiography is the correct approach during laparoscopic cholecystectomy and that, analogous to the current approach to asymptomatic gallstones⁵, silent CBD stones should be left alone.

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Abdominal cramp

Sir

I was interested to learn of Mr Lauste's experience of abdominal cramp (*Br J Surg* 1992; 79: 92). By coincidence, having just been re-reading Zachary Cope's *Early Diagnosis of the Acute Abdomen* (17th ed., 1987), as all good pre-Fellowship trainees, I encountered the following:

'In tropical climes, as a result of great heat and consequent excessive sweating, this may result in a state of salt deficiency. This may give rise to severe cramps which may affect the muscles of the abdominal wall and cause great pain, collapse and rigidity. Diagnosis may be confirmed by measurement of serum electrolytes, and symptoms are resolved with intravenous sodium chloride solutions.'

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Author's reply

Sir

I was pleased to learn that abdominal cramp occurring in tropical heat conditions is mentioned in Zachary Cope's book on the acute abdomen. Curiously, I have found no detailed study or mention of this condition in the literature, although salt depletion in tropical heat is well known. There was no tropical heat in my case and no sweating (although I was told I sweated profusely during the attack). I have considered dietetic salt deficiency, but this must be very rare and unlikely.

During the War I had occasion to look after many Russian prisoners of war suffering from starvation and 'hunger oedema'. They must also have suffered from salt depletion but I never heard mention of muscle cramps or saw this condition.

Incidentally, the altitude of Dhulakel in my original letter should have read 1371 m (4500 ft) and not 13 716 m (at which height hypoxia might have limited the duration of cramp – *Editor*).

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Failed femorocrural reconstruction does not prejudice amputation level

Sir

Tsang *et al.* (*Br J Surg* 1991; 78: 1479–81) are to be congratulated on their enthusiastic efforts towards reconstruction in 450 of 500 patients with limb-threatening leg ischaemia in a 5-year period. The conclusion of their paper was that an unselective policy of vascular reconstruction for critical ischaemia does not lead to a higher proportion of above-knee amputations. They quote a below-knee to above-knee amputation ratio of 2:1 in the group of 50 patients who underwent primary amputation compared with 1:1 in the group of 60 secondary amputations following failed femorodistal bypass. They then claim that direct comparison between the two groups was not valid because they were clinically different. This may be true, but their unqualified conclusions are surely not valid either.

The data presented show that the amputation ratio was in fact 2:1

Correspondence

or worse if a bypass graft failed within 3 months, so from their own data it appears that early failure of a bypass graft before the leg has healed may well lead to a higher level of amputation. Later on, when the leg has healed, it is hardly surprising that failure does not compromise the amputation level.

The enthusiastic approach to limb salvage adopted by the authors is to be applauded, but the suspicion that early femorodistal bypass graft failure leads to a higher level of amputation remains.

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Authors' reply

Sir

We thank Mr Beard for his interest in our paper. Direct comparison between primary and secondary amputation within a single series is not valid because of the obviously different severity of the underlying disease. A randomized prospective trial comparing primary below-knee amputation with distal reconstruction for patients with critical ischaemia would be the only definitive method of settling the question of whether failed femorodistal bypass leads to a higher level of amputation than would otherwise have been necessary. It is our belief that more above-knee amputations will result from primary amputation because of the failure of severely ischaemic below-knee stumps to heal.

Our overall figures combining primary and secondary amputation show 59 below and 41 above the knee, a ratio of 1.4:1 (not 2:1 as Mr Beard states). This ratio compares favourably with data from published series despite our following an unselective policy for distal reconstruction. The suspicion that failed femorodistal reconstruction may lead to a higher level of amputation cannot be used as an excuse to perform primary amputation; this was the intended message of the paper. We believe that the data presented support our conclusion that an enthusiastic approach to limb salvage will not lead to a high incidence of above-knee amputation in patients with failed grafts.

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Role of salivary epidermal growth factor in the pathogenesis of Barrett's columnar lined oesophagus

Sir

I read with interest the article by Gray *et al.* (*Br J Surg* 1991; 78: 1461-6) on the role of salivary epidermal growth factor (EGF) in the pathogenesis of Barrett's columnar lined oesophagus. The main finding of the paper, that salivary EGF does not identify those who will subsequently develop malignant change, corroborates our previously published work, albeit indirectly¹.

In this connection we have previously reported that mucosal concentrations of EGF, determined immunohistochemically, did not differentiate either the metaplastic type of Barrett's mucosa or the degree of tissue dysplasia¹. In the same publication we reported that the expression of transforming growth factor alpha (TGF- α) and EGF receptor were significantly raised in intestinal-type Barrett's mucosa, dysplastic mucosa and individuals with Barrett's adenocarcinoma. We have also demonstrated that flow cytometric analysis of the expression of TGF- α and EGF receptor can be a useful clinical adjunct to the diagnosis and assessment of prognosis of Barrett's mucosa².

Although Gray *et al.* cite many reports of the importance of the proposed trophic action of EGF on intact mucosa via the luminal route in rats, in our experience this seems unlikely in the human oesophagus because the proliferative compartment in Barrett's mucosa is not immediately juxtaposed to the lumen. In addition, those superficial cells that are in the upper third of the glands are usually terminally

differentiated (and not engaged in cell division) and therefore lack EGF receptors and in any case are

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Authors' reply

Sir

Dr Jankowski has rather missed the point of our paper. We clearly stated our view that low levels of salivary epidermal growth factor (EGF) predispose to oesophageal mucosal ulceration owing to a defect in the repair mechanism (cytoprotection) of the squamous epithelium damaged by gastro-oesophageal reflux and hence predisposed to columnar metaplasia. These data¹ have been available since January 1991 and bear no relationship to Dr Jankowski's subsequent immunocytochemical study of columnar metaplasia, which relies on the inevitably subjective interpretation of immunostaining intensity.

We would like to draw Dr Jankowski's attention to our proposed method of improving quantification of immunocytochemistry using computer-aided image analysis². Although it is difficult to comment on the unpublished work quoted in his letter, we would like to draw attention to our published data in this field of proliferating cell nuclear antigen expression in columnar lined oesophagus (CLO)^{3,4}. We also feel that unless his data on EGF receptor expression in CLO are truly quantitative and collected over a reasonable period of time, they are unlikely to provide useful prognostic information.

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Pouch-vaginal fistula occurring 13 years after restorative proctocolectomy

Sir

We would like to draw attention to a case that may be of interest to readers. We recently saw, during a regular follow-up visit, a patient with a pouch-vaginal fistula that developed 13 years after restorative proctectomy. The patient was referred to the late Sir Alan Parks in 1977 for restorative proctocolectomy with a preoperative diagnosis of intractable chronic ulcerative colitis of 17 years' standing. At that time she had a fistula *in ano* and a rectovaginal fistula. It was decided to

numbers of viable, sterile isle and ileostomy with preservation of the vessel, that the major report of the surgical specimen confirmed ulcerative colitis, and no dysplasia was found. One year later the rectovaginal and perianal fistulae had healed and the patient underwent restorative proctectomy with a protective ileostomy. After mucosectomy of a long (6–7 cm) rectal cuff, an S shaped ileal reservoir was hand-sutured to the dentate line. Recovery was uneventful, apart from an episode of small bowel obstruction that required laparotomy 2 months later. The ileostomy was closed 3 months after the pouch procedure. As commonly seen in those with an S shaped reservoir with a long efferent limb, the patient needed to catheterize the pouch, but this has been a regular and uneventful practice during the past 13 years. Pouchitis did not develop.

In June 1990 the patient developed a pouch–vaginal fistula and 1 month later underwent laparotomy, at which no fistular track was detected on dissecting the pouch from the posterior wall of the vagina. Symptoms and signs recurred 14 months later, the external opening of the fistula being 7 cm from the fourchette.

Pouch–vaginal fistulation is a major complication of restorative proctocolectomy, the incidence being between 7 and 14 per cent in series from different centres^{1,2}. It may develop early before ileostomy closure or, more commonly, a few months after. The vast majority of these occur at the ileoanal anastomotic level. Aetiological factors in our experience may include extensive rectovaginal dissection, a short rectal cuff and a stapled anastomosis. Treatment is difficult and local procedures, irrespective of the technique employed, fail in about half of cases. Resuturing the anastomosis does not seem to offer better results. The best outcome is achieved in pouch–vaginal fistulae occurring before ileostomy closure. Ultimately in one-third of cases the pouch has to be excised.

This is the first report of late onset of a pouch–vaginal fistula. In this case chronic trauma from self-catheterization of the pouch may have been the cause.

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Seeding of human microvascular endothelial cells onto polytetrafluoro-ethylene graft material

Sir

We were interested to read the paper by Stansby *et al.* (*Br J Surg* 1991; **78**: 1189–92). The authors argued that since both endothelial and mesothelial cells are suitable for vascular cell seeding, the true origin of these cells might be academic. The assumption that mesothelial cells may also protect the seeded vascular graft against unwanted thrombosis is based on reported observations of non-thrombogenic properties like tissue plasminogen activator synthesis and prostacyclin production of these cells^{1,2}. However, human mesothelial cells do also express procoagulant activity. *In vitro* experiments have shown that isolated and cultured mesothelial cells express tissue factor, the activator of the extrinsic pathway of the coagulation cascade. This is one of the known differences between mesothelial and endothelial cells. Therefore, in our opinion, cells harvested from the omental fat should be characterized. Mesothelial cells are identified by staining with monoclonal antibodies directed against cytokeratins 6 and 18, an immunofluorescence staining procedure that can be performed in every laboratory³. Expression of cytokeratins by endothelial cells has never been reported. Because a cobblestone appearance in culture, uptake of diacylated low-density lipoprotein, and positive immunofluorescent staining for von Willebrand's factor used by Stansby *et al.* are also properties of mesothelial cells, the characterization of endothelial cells by these features is far from reliable⁴. With the use of immunofluorescence staining with monoclonal antibodies for cytokeratins, it is now generally accepted that cobblestone cells derived from omental

fat tissue are not endothelial but mesothelial in origin^{4,5}. To prevent further confusion and to stimulate more studies on the suitability of omental cells for vascular cell seeding, reliable characterization of these cells should be undertaken.

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Surgical implications of drug-induced rhabdomyolysis

Sir

We read with interest the paper by Rutgers *et al.* (*Br J Surg* 1991; **78**: 490–2) in which four cases of acute drug-induced rhabdomyolysis with secondary compartment syndromes are described. We agree that drug-induced toxic rhabdomyolysis is uncommon and that many cases are associated with coma which may cause secondary muscle damage. The few drugs that have been implicated in causing direct toxic rhabdomyolysis include alcohol, barbiturates and other psychotropic drugs which have been reviewed comprehensively by Gabow *et al.*¹. We recently reported a case of rhabdomyolysis and compartment syndrome secondary to theophylline overdose².

In the paper cited all the patients were alcoholics but no mention was made of delirium tremens, hypocalcaemia and the toxic effect of alcohol and benzodiazepines, all of which may contribute to rhabdomyolysis. Furthermore, there was no report of the serum levels of calcium, benzodiazepines or alcohol.

Even though the authors rightly point out the value of monitoring compartment pressures, in none of the cases presented was the compartment pressure quoted. We would suggest that pressure monitoring is mandatory when a diagnosis of compartment syndrome is considered in a patient who is unwilling or unable to cooperate in eliciting clinical signs, and that full documentation of serum toxicology is essential when discussing the complications of drug overdose.

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Current management of trauma to the pancreas

Sir

Messrs Wilson and Moorehead attempted an exhaustive review of the management of pancreatic trauma (*Br J Surg* 1991; **78**: 1196–202). Unfortunately, certain laconic statements make the title 'current management' questionable.

1. 'One dose (of antibiotics) before operation should be followed by two doses thereafter unless there is colonic injury, in which case a therapeutic course for 5 days should be used.' This suggestion does not reflect the state of the art. Currently, most trauma surgeons do not recommend antibiotic therapy beyond 48 h after colonic injury¹. In fact, when contamination is minimal, a short perioperative course is satisfactory.

2. 'Some suggest splenic preservation (during distal pancreatectomy), but this involves a tedious dissection and added time, which could be considered inappropriate in an acute situation.' This is not true: using Warsaw's manoeuvre², tedious and time-consuming dissection of the pancreas off the splenic vessels is no longer necessary. Instead the pancreas is separated from the spleen by dividing the splenic artery and vein distal to the pancreatic tail, allowing the spleen to survive on the short gastric vessels. The latter are carefully preserved by staying away from the splenic hilum.

3. The authors dogmatically endorse the use of sump drains which 'should always be used'. Recent articles that question the superiority of these drains in pancreatic trauma are not stated, and topics such as the two-stage pancreaticoduodenectomy and pancreatic 'sequestrum' formation are not mentioned.

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Authors' reply

Sir

We disagree with the criticisms by Dr Schein of our paper.

1. A short perioperative course of broad-spectrum antibiotics is appropriate with minimal contamination from colonic injury. A therapeutic course is the policy of ourselves and most others if there is major contamination.

2. The technique described by Warsaw for splenic preservation involves sacrifice of the splenic artery and vein¹. Ligation of the splenic artery may not protect against overwhelming postsplenectomy infection as there is evidence that it impairs pneumococcal clearance². This type of splenic preservation has no clear benefit and is inadvisable in the acutely-injured patient.

3. We reviewed all the recent English language literature for the article and found that the vast majority of authors endorse our view that sump drains should be used in pancreatic trauma.

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1. Warsaw AL. Conservation of the spleen with distal pancreatectomy. *Arch Surg* 1988; **123**: 550-3.
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Surgical training: a report to the Association of Surgeons of Great Britain and Ireland

Sir

The continuing debate on surgical training in Great Britain and Ireland is being followed with avid interest in many parts of the world, not least in the Commonwealth countries whose surgical training and traditions closely follow the British school.

The report by Professor Jones (*Br J Surg* 1991; **78**: 1156-8) highlighted many of the problems of the current training programme, and proposed solutions. He noted the difficulty being encountered by trainees in Great Britain and Ireland in acquiring the necessary

exposure to conventional procedures in gastrointestinal surgery in the light of recent advances in endoscopic techniques and changes in the pattern and presentation of these diseases. This difficulty is further compounded by the requirement of The Royal College of Surgeons of England for surgeons undertaking laparoscopic surgery to be competent in the standard techniques.

I should like to suggest that this problem can be solved if trainees in Great Britain and Ireland spend time in hospitals in the developing countries where the bulk of gastrointestinal surgery still uses open methods. In this way, their requirement for training in conventional techniques will be satisfied, an avenue will be created for exchange of ideas and contacts (necessary for the continual growth of surgical disciplines worldwide) and those in surgical departments in the developing world who have benefited from the Overseas Doctors Training Scheme will derive a sense of accomplishment in providing what is 'lacking' in the training programmes in Great Britain and Ireland.

The Royal Colleges can identify appropriate surgical departments and establish methods of monitoring to ensure that such a scheme satisfies the need that produced it.

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Aggressive arterial reconstruction for critical lower limb ischaemia

Sir

We read with interest the paper by Hickey *et al.* (*Br J Surg* 1991; **78**: 1476-8), in which they report on their excellent results for femorocrural surgery. I can confirm that these results are entirely achievable but would point out that the authors' insistence that the results can be obtained without angiographic selection is somewhat dependent on local factors in Birmingham. The reason that the group does not use angiography before operation is that they do not routinely offer angioplasty to such patients. In our own practice an angiogram as a first investigation is mandatory simply because it will reveal a large number of patients who can be dealt with in this way. In our own practice this is now 40 per cent of such cases. When these patients have undergone successful angioplasty, the remainder that are available for surgical treatment are those cases with very poor run-off. The series of Hickey *et al.* therefore includes such 'good' patients who would normally not come to surgery. While applauding their good results, we would caution that an angiogram is important and that angioplasty should be made available to these patients as it can either obviate the need for surgery or improve inflow in some cases.

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Authors' reply

Sir

We agree with Professor Bell and Mr London that many patients with symptomatic femoropopliteal occlusive disease can benefit from transluminal angioplasty. However, in our patients with unequivocally critical lower limb ischaemia and a satisfactory femoral pulse, we proceed straight to operative arteriography and it is extremely rare for this to reveal an anatomical situation that could conceivably be relieved by transluminal angioplasty alone, even in the most expert hands.

In patients with less severe symptoms or those in whom femoral pulse palpation suggests inflow disease, we do obtain preoperative arteriograms as many of these patients will benefit from a percutaneous procedure as Messrs Bell and London suggest.

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Experimental and Clinical Liver Transplantation

R. Engemann and H. Hamelmann. 246 × 170 mm. Pp. 254 + xii. Illustrated. 1991. Amsterdam: Elsevier.

This monograph brings together the proceedings of the international workshop on experimental and clinical liver transplantation held in Wilsede in May 1990, with a primary emphasis on experimental laboratory-based evaluation of rejection, infection and immunoregulation.

While most intimate workshops and symposia on specialist subjects have their own aura and interest, it is often difficult to capture this in brief monographs from the presentations. The amount of clinical data incorporated within this monograph is limited, and emphasis on the experimental aspects of liver transplantation is paramount. While forming a useful compendium of data, a lot of the information is not new and comprises in some parts a summary or overview. Nevertheless, some of the sections are valuable, particularly that on immunology, which includes a review of cell-mediated suppression.

To the experimental worker with a primary laboratory-based interest, this will form a useful update on current experimental studies, but it is unlikely to have a wider interest to the clinician confronted with the day-to-day problems of liver transplantation services. This book is a useful addendum to the laboratory shelf but not a vital component of every library.

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Vascular Surgery – Current Questions

A. A. B. Barros D'Sa, P. R. F. Bell, S. G. Darke, P. L. Harris (eds). 170 × 240 mm. Pp. 250. Illustrated. 1991. Oxford: Butterworth-Heinemann. £49.50.

Vascular surgery has been eager to embrace new technology such as percutaneous atherectomy and angioplasty, but critics comment that these innovations are often introduced without objective and critical evaluation. In 1983 the Joint Vascular Research Group (JVRG) was formed with the intention of entering as many patients as possible into collaborative evaluations of vascular operations and their outcome. One of the group's early and most successful studies examined the natural history of critical ischaemia of the lower limb over a 3-year period.

The book is the result of a major symposium held by the JVRG in Belfast last year. It provides a candid 'snapshot' of vascular surgical practice in the UK. The questions addressed are practical and confront clinicians every day in theatre, on the wards and in the outpatient department. The initial reaction to a book with four editors, 19 contributors and only 250 pages is that there is a lack of cohesion and consistent style. Paradoxically, I think this is one of the book's strengths. There are very few 'right' ways of doing things and it is refreshing to discover a personal ethos in each contribution rather than the usual 'party line'. There are useful critical reviews on renovascular disease, risk factors and sepsis. The chapter on femorodistal bypass is a lucid distillation of the best of British research and that on carotid surgery touches on natural philosophy, clinical trial design and patient selection; it makes entertaining reading. The contribution on deep vein thrombosis is an excellent summary for those taking the final FRCS examination.

Overall this is a book with wide appeal; it would be of most use to practising surgeons, physicians interested in vascular disease or those training in vascular surgery. One drawback is that some writers describe approaches that may be restricted by local circumstance – for example, the chapter on the clinical vascular laboratory makes little reference to venous assessment. A second drawback is the price, which is a disincentive to purchase a book that deserves a broad readership.

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Basic and Clinical Biostatistics

B. Dawson-Saunders and R. G. Trapp. 260 × 180 mm. Pp. 329 + ix. Illustrated. 1990. Norwalk, Connecticut: Appleton and Lange.

This book is co-authored by a biostatistician and a clinician, and successfully deals with the particular needs and viewpoints of practising doctors. Despite its cheery bright paperback exterior it is a scholarly work of substance. It contains the expected chapters on probability, means, proportions, correlation and regression, analysis of survival data, and multiple variables, and I am sure that any medical statistical query I have ever had is answered in these authoritative pages. Although it is not a lightweight volume, it is quite easy for the statistical novice to understand as terms are clearly defined, calculations kept to a minimum, and problems dealt with in a genuine medical context.

Other chapters deal with study design in medical research, drawing inference from data, evaluating diagnostic procedures, clinical decision-making, and reading medical literature. It is also recognized that today all researchers use computers to analyse data and the authors go to some length to advise on reading and interpreting computer analyses.

Many books on medical statistics, in an attempt to be 'reader-friendly', are too superficial and tend to be unsatisfactory when used to obtain practical help. Other texts, written by statisticians for statisticians, can be near incomprehensible to most medical students and clinicians. *Basic and Clinical Biostatistics*, on the other hand, is just right for most practising doctors. The authors are to be congratulated on a fine piece of work which should have a wide appeal.

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A Text and Atlas of Liver Ultrasound

H. Bismuth, F. Kunstlinger, D. Castaing. 200 × 285 mm. Pp. 140. Illustrated. London: Chapman and Hall. £55.

This book is written by two surgeons and a radiologist and has been translated from the original French. As its title suggests, it is not only a textbook but also an atlas and it contains many high-quality ultrasonography images. The French authors are well known ultrasonography enthusiasts, applying the technique widely to hepatic surgery. Other techniques such as computed tomography and magnetic resonance imaging are discussed with up-to-date references.

The ten chapters deal with all aspects of liver ultrasonography, covering normal anatomy, focal and hepatocellular disease, the intrahepatic biliary tree and liver vascularity. There are specific chapters relating to intraoperative ultrasonography, interventional ultrasonography and liver transplantation. All of these are written clearly and concisely, covering the topics thoroughly. There is, however, some duplication of material in the chapter on liver ultrasonography and the oncologist. The accompanying references, mostly from English language journals, are recent and together with the text represent 'state-of-the-art' views on hepatic ultrasonography. The translation is generally excellent with one exception: the word 'image' is used in places to refer to an abnormal area or lesion within the actual image.

This well written and elegantly illustrated text is to be recommended to general surgeons and physicians, as well as to ultrasonographers in training from whatever specialty, for whom it provides a concise description of the diagnostic capabilities of ultrasonography in liver disease. It will also appeal to hepatobiliary surgeons wishing to add the relatively new tool of intraoperative ultrasonography to their armamentarium.

I have one word of warning that is perhaps overlooked in the text. The book describes what ultrasonography can achieve when performed at its best by dedicated exponents; this is reflected in the quoted comparative studies between ultrasonography and other techniques. One should never forget that the results obtained from ultrasonography are totally operator dependent and that image resolution is very much better in thin than in obese patients.

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Surgery of Liver Disease in Children

E. R. Howard (ed.). 195 × 252 mm. Pp. 242. Illustrated. 1991. Oxford: Butterworth-Heinemann. £75.

This is a most welcome and valuable book. The past two decades have seen significant advances in many aspects of paediatric liver surgery including an understanding of the segmental anatomy of the liver, the development of portoenterostomy for biliary atresia, the use of sclerotherapy to control variceal bleeding, and the role of liver transplantation. Whereas there have been numerous texts dealing with progress in adult surgical conditions, these have paid limited attention to paediatric aspects. This book redresses the balance by providing a comprehensive review of current management on the whole range of childhood surgical liver disorders.

As well as anticipated chapters on biliary atresia, portal hypertension, surgery for hepatic tumours and liver replacement, other useful contributions include physiology and anaesthesia, liver trauma, and chemotherapy for tumours. The editor should take credit not only for writing the majority of the chapters himself but for producing a free-flowing text that includes contributions from France and Japan. The book is well illustrated with high quality black-and-white photographs, although there is no uniformity of style in the line diagrams; these would benefit from revision when the next edition is produced. This book will be bought and treasured by surgeons who treat children with liver disease.

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General Thoracic Surgery. 3rd ed.

T. W. Shields (ed.). 225 × 285 mm. Pp. 1251. Illustrated. 1989. Philadelphia: Lea and Febiger. £105.

This is the third edition of what has become a standard general thoracic surgery text. It has been thoroughly updated and achieves its stated aim of being an extensive coverage of the specialty.

Twenty-five new chapters have been incorporated since the second edition, with important topics such as computed tomography, magnetic resonance imaging and jet ventilation now being covered. A full section is devoted to thoracic trauma, with separate chapters on: trauma to the chest wall, pleura and thoracic viscera; adult respiratory distress syndrome; management of foreign bodies of the upper aerodigestive tract; trauma to the oesophagus; and diaphragmatic injuries. I found this section of the book contained particularly worthwhile additions to previous editions. While all topics in thoracic surgery are to a greater or lesser extent covered, emphasis is perhaps on occasion not totally suited to contemporary issues. For instance, although the volume contains over 1250 pages, only 12 are devoted to lung transplantation. I would have liked a full section on this important topic, particularly as it is of interest to the younger surgeon and those in training. The final three sections of the book have, by the strictest of criteria, a non-surgical content. They are devoted to radiation therapy, chemotherapy and immunotherapy, and much of the information in them is essential knowledge for the thoracic surgeon. However, illustrations in these sections are relatively scanty and the writing style often somewhat disparate compared with the rest of the volume.

While the editing is extremely skilful, this book suffers the problems seen generally with multiauthor volumes, particularly as regards continuity and, in a few cases, repetition. The illustrations are generally excellent throughout, although all are in black and white. The volume is well referenced, although many of these are somewhat historical with very few from the past 5 years. This no doubt reflects the time necessary to prepare such a large volume.

I would unhesitatingly recommend this volume to any thoracic or indeed aspiring thoracic surgeon. It is a reference work and not an easy read as a volume, but for reference to a particular topic it is most useful. Librarians of all postgraduate medical libraries with a surgical readership should consider this a suitable purchase for their shelves.

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On Narcotism by the Inhalation of Vapours

J. Snow with an introductory essay by R. H. E. Snow. Pp. 142. Illustrated. 1991. London: Royal Society of Medicine Press. £12.50.

John Snow was many decades ahead of his time. His epidemiological studies during the 1849 and 1854 outbreaks of cholera in London, culminating in the proof that cholera is a water-borne infectious disease, are known to every medical student. His work on inhalational anaesthesia is less well known, but no less impressive.

Between 1848 and 1852 Snow published, in the *London Medical Gazette*, a series of articles that described his experimental, clinical and philosophical observations on the use of inhalational anaesthetic agents. The articles were later republished as pamphlets, and this lovely book brings together the collected pamphlets in facsimile form. In his introduction, Richard Ellis speculates that Snow was searching through the *London Medical Gazette* of 18 December 1846 for his own case report of ileal strangulation by a mesenteric defect, when he came across the first UK account of the invention of anaesthesia in Boston, Massachusetts. Within days, he had witnessed ether anaesthesia for himself. Eighteen months later Snow began to publish his own work, which included detailed animal experiments on both qualitative and quantitative aspects of inhalational anaesthesia. He quickly realized that it was vital to control the rate of administration of ether and chloroform, and he designed a vaporizer. When accounts of anaesthesia-related deaths came from Newcastle, Cincinnati, Boulogne and Hyderabad, he was able to analyse them critically and explain their causes. Snow included fascinating case reports on anaesthesia for lithotomy, breast cancer, maxillary and orthopaedic surgery, and to facilitate clinical examination. He offered advice on preoperative fasting, and made an early contribution to audit by publishing mortality rates for major amputation under anaesthesia. This he did to allow comparison with data from surgery without anaesthesia, at the same time acknowledging the inadequacy of historical controls. Snow expressed disdain for social drinking, but took wine himself as part of an extraordinary series of experiments to compare the effects of alcohol with those of ether and chloroform. In the course of these experiments he proved, using his own design of 'breathalyser', that alcohol is excreted in the breath.

I found this book enormously enjoyable, not only for its historical insights but also for the intellectual clarity and scientific rigour exhibited by John Snow. A second copy would make an excellent gift for your favourite anaesthetist.

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Comprehensive Atlas of Lumbar Spine Surgery

H. Tsuji. 219 × 285 mm. Pp. 327. Illustrated. 1991. St Louis: Mosby-Year Book. US \$129.

Professor Tsuji is one of the leading spinal surgeons in Japan and his Atlas is based on personal experience over the past 30 years. The book sets out to illustrate aspects of spinal surgical technique with comprehensive line drawings, prepared by the author himself. The result can be highly recommended for the young surgeon. Orthopaedic surgeons in the UK may find it surprising that techniques relating to the treatment of spinal tumours are included; traditionally, Japanese orthopaedic surgeons have always managed tumours and spinal vascular malformations.

I have only two minor criticisms. First, there is an undue emphasis on the use of fat grafts following exploration of the spinal canal. Second, in relation to anterior interbody fusion techniques, the surgical approaches that the author depicts, involving section of the abdominal muscles, have been largely replaced either by approaches through the rectus sheath itself or by lateral muscle-splitting incisions of the type described by Frazer from Adelaide.

Overall, this is an excellent monograph that has been very ably translated into English by Professor Edgar Dawson of the UCLA School of Medicine.

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Book review: *Anatomy*

ureau, A. Dixon. 197 × 289 mm. Pp. 304. Illustrated. Worth-Heinemann. £55.

Interpreting results of modern imaging methods requires a knowledge of sectional anatomy. This applies not only to the imaging specialist but also to the referring clinician who wishes to make use of the relevant hard copy images. While computed tomography (CT) involves predominantly axial sections, the versatility of magnetic resonance imaging (MRI) requires an in-depth consideration of coronal and sagittal sectional anatomy.

The authors of this atlas of CT and MRI radiological anatomy have chosen the combination of images with matched line drawings, rather than the alternative approach of images with corresponding cadaver sections. An additional plan drawing explains the image plane and its angulation. The images are of high quality throughout and the accompanying line drawings detailed, accurate and explicit. The end result is 'user friendly' and allows easy orientation to the plane of anatomy. One is unaware of this having been translated from another language.

The major anatomical areas of pathological interest are covered in 13 chapters; imaging parameters are presented at the beginning of each. While the central nervous system is well covered, elsewhere there is an imbalance of images in favour of CT. This is particularly so for the spine where one might expect greater emphasis on MRI, both in terms of anatomy and of pulse sequences. However, it must be recognized that the pace of development in magnetic resonance techniques makes it very difficult to publish the 'state of the art'. Overall, this is a well presented and practical atlas that can be recommended as a useful reference source; quality and user friendliness are its strong points.

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Trauma. 2nd ed.

E. E. Moore, K. L. Mattox, D. V. Feliciano (eds). 215 × 280 mm. Pp. 1009. Illustrated. 1991. USA: Appleton and Lange.

With the rapid development of new diagnostic and therapeutic techniques in trauma care, no textbook could be described as representing the 'state of the art'. However, the second edition of *Trauma* is probably the closest realization of this moving goal available. The editors, themselves well known internationally in the field of trauma care, have chosen contributors whose names are familiar from pioneering research over the past 10 years. In doing so, they have produced a credible and valuable reference text.

Although sweeping changes have taken place in the definitive surgical management of specific injuries, basic principles of resuscitation remain the same. The initial chapters provide a good account of the painful lessons that have been learned again and again over the centuries, usually in times of war. The following chapters take the reader through initial assessment of the traumatized patient, including management of the airway, breathing and circulation, in a didactic fashion. There are some general chapters on topics such as the management of shock, radiology, and anaesthesia in the traumatized patient.

Although most discussions of technique are included within chapters on specific injuries, there is an important individual chapter on emergency department thoracotomy. This technique has undergone a revival during the past decade, particularly to provide access for open cardiac massage and definitive surgery. It has a well defined place in the treatment of penetrating injury, and this chapter gives an extensive review of recent work, advocating a selective application.

Management of specific injuries is detailed and supported by up-to-date research. There are interesting and well constructed chapters on different types of social violence, organ retrieval and transplantation, reconstructive surgery, and rehabilitation. The section on the medicolegal aspects of trauma, although pertaining to a different legal system, is fascinating. With the changes in our own health service, it is interesting to see unravelled the process of legislation covering the less well off trauma patient without insurance in the USA. Unfortunately, the legal relationship between physicians and paramedic ambulance staff is not explored in any detail.

Inevitably, a text of this size written entirely by North American

authors contains some advice not applicable in western Europe. For example, one author, in discussing sedation, states that he would not favour the use of benzodiazepines because there is no effective antagonist available. It appears that flumazenil is not licensed for use yet in the USA whereas it has been in regular use in Europe for a number of years.

Taken as a whole, this is probably the best reference text covering the field of trauma available at present, and I would recommend it for the libraries of all hospitals with trainee surgeons on their staff.

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Patient Care in Colorectal Surgery

D. E. Beck, D. R. Welling (eds). 133 × 215 mm. Pp. 351. Illustrated. 1991. USA: Little, Brown Medical. £29.

This is a most interesting book; it is also highly irritating. The reason it is irritating is that the editors have not decided for whom the book is written – they have written it for everyone. This means that the chapter on anatomy contains such statements as 'the colon (large intestine)', and 'the colon contains two flexures (or bends)'. Surely anyone likely to pick up this book will know what the colon and its flexures are.

The chapter on pathophysiology is excellent so far as it goes, but it omits the anorectal physiology investigation of incontinence and thus fails to discuss pudendal neuropathy. Likewise the chapter on radiology, in which I particularly like the acceptance by the two radiologist authors on the erect and supine abdomen, in recognition that plain radiographs of the abdomen in the emergency setting are usually interpreted by surgeons. Although this is a book on colorectal surgery, the proffered radiographs are of gallstones, livers, subphrenic abscesses and even magnetic resonance images of metastatic gastric cancer. Proctography is described scantily and anal imaging (e.g. ultrasonography, magnetic resonance imaging, fistulography) completely ignored. It is unfortunate that the radiographs are reproduced so poorly but this is in line with the rest of the production.

However, there are also gems: 'Is there anything about your sexual lifestyle that could be important for me, as your physician, to know so that I can best treat your condition?' and 'vocal anaesthesia' in the chapter on endoscopy. There are also some very well known authors who have contributed thoughtful articles. In summary, as it is this book may be a reasonable buy but with tighter editing it would be a read.

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Investigation of Patients with Deep Vein Thrombosis and Chronic Venous Insufficiency

A. N. Nicolaidis and D. S. Sumner. 169 × 239 mm. Pp. 80. Illustrated. 1991. London: Med-Orion. £28.50.

This is a nicely done little book that is well produced and referenced. It would have little relevance for the ordinary general surgeon, but is a useful reference work for researchers interested in the scientific investigation of venous disease. Many of the investigations are covered in standard venous textbooks, but this monograph puts them together in a simple and easily readable form. It contains good examples of duplex scans and some reasonable venograms. Emphasis is placed on, air plethysmography, as one might expect from Professor Nicolaidis, and my only quibble would be with his persistent attempts to define the haemodynamically important perforating veins by drawing imaginary boxes around dotagrams.

This is a book for the connoisseur rather than the journeyman, but I can certainly recommend it to all those interested in venous disease.

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Plastic and Reconstructive Breast Surgery: an Atlas

G. Lemperle, J. Nievergelt. 200 × 275 mm. Pp. 192. Illustrated. 1991. Heidelberg, Germany: Springer-Verlag. DM 298.

Although this atlas contains numerous well produced colour pictures of the full range of plastic and reconstructive procedures of value in breast disease, it is unfortunate that the text strays into the field of oncology. The statement that 'complete removal of the mammary gland is always indicated for cancerous and precancerous disease' is totally unsupported by the literature and unacceptable. Advice that 'general anaesthesia is indicated in any patient with a breast lump where there is the least suspicion of malignancy' betrays a disturbing lack of knowledge of currently available non-operative diagnostic techniques. There are also other areas of concern that include recommending unilateral mastectomy for localized lobular carcinoma *in situ*.

Some illustrations refer to historical procedures and this appears to have restricted the space available for many of the more sophisticated techniques used today. There certainly should have been greater discussion and more detail about the rectus abdominis flap. Having said this, many topics are well covered and it is clear from reading the book that the authors have a wealth of experience.

As the investigation and treatment of invasive and non-invasive breast cancer recommended by the authors are not consistent with current informed opinion, this book will at the very least confuse readers and may actually mislead them.

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Clinical Measurement in Coloproctology

D. Kumar, D. J. Waldron, N. S. Williams (eds). 197 × 276 mm. Pp. 230. Illustrated. 1991. Heidelberg, Germany: Springer-Verlag. DM 180.

This well presented book sets out to bring physiological assessment of the colon, rectum and anal canal into the remit of the non-specialist clinician. Many of the complexities of the investigative techniques are concisely explained in the opening section and will lead to a greater appreciation among readers in general about the importance of this expanding field, both in elucidating the underlying pathophysiology of disorders and in the physiological rationale behind advances in their treatment. For the specialist there are succinct accounts of the latest investigative processes at the advancing borders of this field. One criticism might be that the accepted standard and the highly specialized investigations are intermixed; the distinction is not always clear. In fact, a good opportunity to include a chapter on the arrangement of a basic physiological laboratory has been missed and this does detract slightly from the overall effect. The value of the investigative techniques is, however, highlighted by the sections on coloproctological disorders and postoperative function, all written by experts in their fields. The explanations in these sections add greatly to the value of the book by integrating the results of investigations into clinical practice.

Overall this book should enjoy a wide readership and successfully fill a major gap in the literature. It is highly recommended to trainees and general clinicians with an interest in coloproctology and contains many areas of interest to the specialist coloproctologist.

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Multiple Organ Failure: Patient Care and Prevention

A. E. Baue. 185 × 272 mm. Pp. 574. Illustrated. 1990. St Louis: Mosby-Year Book. £59.25.

This textbook is a single-author work, with the exception of a short chapter written by the author's wife. Single authorship is perhaps a little surprising given the subject matter of the book but it would be difficult to imagine an individual better qualified for the task: Arthur E. Baue first described a syndrome of multiple, sequential, or progressive systems of organ failure in 1975. The author tells us that the book grew from a series of lectures backed up by a perspective of the literature, which he gained working for 12 years as editor of *Archives of Surgery*.

The text is divided into six main sections. The first describes the biological response to injury and is followed by a section detailing surgical factors in the perioperative period that may set the scene for multiple organ failure. The third section deals specifically with trauma. Section 4 comprises a lengthy description of dysfunction in individual organ systems while the final two sections deal with multiple organ failure itself.

The general style of the text is conversational, making for easy reading. It is probably fair to say that the publication date, together with single authorship, have contributed to a relative lack of up-to-date references when describing some aspects of the multiple organ failure syndrome. This is perhaps most obvious when reading descriptions of areas in which rapid advances are currently being made, notably the immunotherapy of sepsis and prevention of infection. This is not a suitable text for the research fellow or student looking for up-to-date referencing in the field of multiple organ failure. However, it is an excellent and very readable overview of the subject, focused from a surgical viewpoint.

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Pancreatic Disease - Progress and Prospects

C. D. Johnson, C. W. Imrie (eds). 167 × 248 mm. Pp. 380. Illustrated. 1991. Heidelberg, Germany: Springer-Verlag. DM 146.

The editors of this book have persuaded the speakers at a recent meeting to contribute chapters written as up-to-date reviews in areas of pancreatic disease where progress has been made. The result is a stimulating collection of readable chapters that cover a wide spectrum of pancreatic problems including cystic fibrosis, pancreatic surgery in childhood and pancreatic transplantation. Pancreatitis and pancreatic malignancy are well represented with contributions including practical guidance in surgery and therapeutic endoscopy and radiology. The chapters are concise, appropriately illustrated and well referenced. The views expressed are impressively up to date and the editors are to be congratulated on producing the book so quickly. The contents span the interests of several disciplines and I am certain that the book will appeal to all those with an interest in pancreatic disease. Readers will undoubtedly find something to stimulate further their interest in pancreatic problems.

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September 1992

Ultrasound Angiography '92 *Southampton, UK*

Information: Secretariat, Ultrasound Angiography '92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK

9-11 September 1992

2nd Nottingham International Breast Cancer Meeting *Nottingham, UK*

Information: Mrs Wendy Bartlam, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

10-11 September 1992

Association of Anaesthetists of Great Britain and Ireland Annual Scientific Meeting *Bournemouth, UK*

Information: Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA, UK

14-15 September 1992

Oxford Paediatric Trauma Conference *Oxford, UK*

Information: Mr M. Williams, 6 Huntsman's Close, Badsworth, West Yorkshire WF9 1BE, UK

20-23 September 1992

VIIth Edmondo Malan International Day of Surgery - Endo-laparoscopic and Mini-invasive Surgery *Parma, Italy*

Information: Professor Gian Carlo Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43100 Parma, Italy

20-24 September 1992

Combined Meeting of the Association of Surgeons of Great Britain and Ireland and Trinity College Dublin Quatercentenary Meeting *Dublin, Ireland*

Information: Mr T. N. Walsh, Department of Surgery, St James's Hospital, Dublin, Ireland

22-24 September 1992

Fifth Meeting of the International Association of Pancreatologists and Fourth Meeting of the International Pancreatic Cancer Study Group *Athens, Greece*

Information: Congress Secretariat, Dr C. Arvanitakis, First Medical Department, University of Thessaloniki, AHEPA General Hospital, 54 006 Thessaloniki, Greece

24-26 September 1992

Postgraduate Course - Principles of Colon and Rectal Surgery *Minnesota, Minneapolis, USA*

Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue Southeast, Minneapolis, Minnesota 55414, USA

7-8 October 1992

VIIth National Conference of the Association of Paediatric Surgeons of Pakistan *Lahore, Pakistan*

Information: Dr Z. B. Attar, Department of Paediatric Surgery, National Institute of Child Health, Karachi, Pakistan

8-9 October 1992

Second GI Tract Laparoscopic Surgery International Meeting *Liège, Belgium*

Information: Catherine Marissiaux, Clinique St-Joseph, Chirurgie de l'Appareil Digestif, Rue de Hesbaye 75, B-4000 Liège, Belgium

15-16 October 1992

European School of Oncology 10th Anniversary Events *Milan, Italy*

Information: European School of Oncology, Via Venezian 18, 20133 Milan, Italy

23 October 1992

Symposium-Extracranial Carotid Artery Surgery: Including Prevention of Stroke *London, UK*

Information: Mrs Louise Brooks, Meadox UK Ltd, Matthew House, Matthew Street, Dunstable LU6 1SD, UK

27 October-4 November 1992

Anaesthesia and Surgical Intensive Care: Controversies and Conflicts *Bristol, UK*

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

4-8 November 1992

American Association for Cancer Research-Genetics of Cancer *Hilton Head Island, South Carolina, USA*

Information: American Association for Cancer Research, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, PA 19106-3483, USA

6-7 November 1992

International College of Surgeons 38th Annual Meeting of the Japan Section - 'Controversies in Surgery' *Tokyo, Japan*

Information: Professor K. Kimura, Department of Surgery, Tokyo Medical College, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan 160

15-18 November 1992

Update and Future Trends in Fibrin Sealing in Surgical and Non-surgical Fields *Vienna, Austria*

Information: Univ. Prof. G. Schlag, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstraße 13, A-1200 Vienna, Austria

15-21 November 1992

Advances in Cancer Treatment *London, UK*

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

16-20 November 1992

Research Methods in Surgery *London, UK*

Information: Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

16-21 November 1992

XXVIII World Congress of the International College of Surgeons *Cairo, Egypt*

Information: EMECO Travel, 2 Talaat Harb Street, PO Box 1294, Cairo, Egypt

25-28 November 1992

Recent Advances in Anaesthesia, Pain, Intensive Care and Emergency *Trieste, Italy*

Information: Trieste Traduzioni Congressi, Via C. Battisti 1, 34125 Trieste, Italy

3-5 December 1992

Special International Columbus Meeting on Surgical Oncology *Genoa, Italy*

Information: Italiana Congressi, Via P. E. Bensa 2/6A, 16124 Genoa, Italy

4-5 December 1992

8th International Steglitz Paediatric Surgical Congress: Endoscopic Surgery in Children *Berlin, Germany*

Information: Dr F. Schier, Kinderchirurgie, Universitätsklinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany

8-10 December 1992

Seventh International Workshop on Therapeutic Endoscopy *Hong Kong*

Information: Dr S. Chung, Combined Endoscopy Unit, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

10-11 December 1992

Reconstruction in Surgical Oncology *Genoa, Italy*

Information: Anna Guida, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10-16132 Genoa, Italy

3-6 January 1993

Postgraduate Course in Gastroenterology *Oxford, UK*

Information: Dr D. P. Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

7-8 January 1993

Surgical Research Society Meeting *London, UK*

Information: Professor J. R. Farnon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK



SURGERY

Official Publication

**SOCIETY OF UNIVERSITY SURGEONS, CENTRAL SURGICAL ASSOCIATION,
and AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS**

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Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

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Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

Continuing our report on the Officers and Members of Council of the Society that administers the Journal, we present the three privileged Members who represent our three affiliated bodies: the Royal Colleges of Surgeons in the British Isles, the Association of Surgeons of Great Britain and Ireland, and the Surgical Research Society.

Representative of the Royal Colleges of Surgeons

PROFESSOR OLEG EREMIN

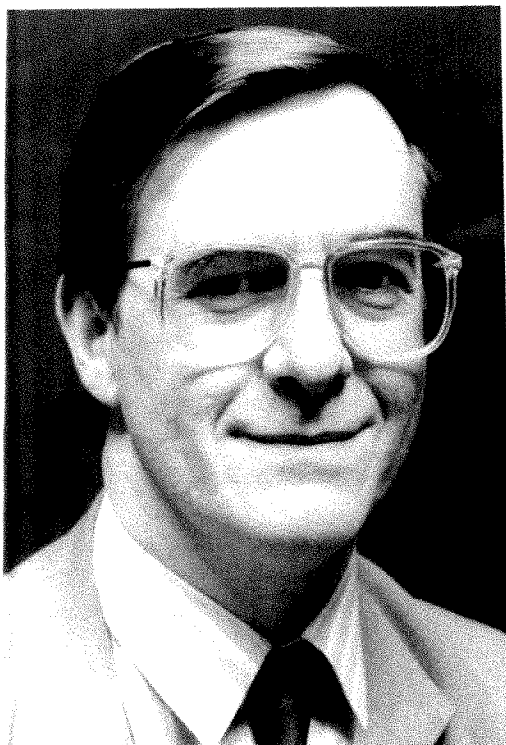


Oleg Eremin, who was born in 1938 and is of Australian nationality, is Regius Professor of Surgery in the University of Aberdeen. He graduated as a doctor at Melbourne in 1964 and spent the next 5 years climbing the surgical ladder in that city. His training was punctuated by a 6-month attachment at Port Moresby in New Guinea where, his curriculum vitae attests, he had 'exposure to trauma and tropical disease'. Surviving this experience he was translocated to the wilds of East Anglia, spending time as a senior registrar at Norwich (1972-1974) and Huntingdon (1980). In between he was a senior research associate in the Department of Pathology at Cambridge University, where he pursued

his particular interest in tumour immunology. In 1989 he became a consultant senior lecturer under Sir Patrick Forrest at Edinburgh, and he continued this northwards migration to take up his present post in 1985. To his FRACS (1971) was added the FRCS (Edinburgh) in 1983 and an MD (Melbourne) in 1985. Professor Eremin is a general surgeon with a strong clinical interest in oncology, notably breast cancer, colorectal cancer and melanoma. He has examined widely in the UK and the Middle East and is a member of some 15 different surgical societies. He joined the Council of The British Journal of Surgery Society in 1990.

**Representative
of the Surgical Research Society**

PROFESSOR ROBERT MANSEL



Robert Edward Mansel (born 1948) has been Professor of Surgery in the University of Manchester since 1989 but will be taking up the Chair of Surgery at the University of Wales College of Medicine in succession to Professor L. E. Hughes later this year. In 1971 Bob Mansel qualified at Charing Cross Hospital Medical School, where he won the Morgan Evanson Scholarship and undertook junior surgical posts. Moving down the M4 motorway he reached Swindon as a surgical registrar in 1974 and then Cardiff in 1976, where he progressed from research fellow to senior registrar to clinical lecturer to senior lecturer (appointed 1983). He obtained his English Fellowship in 1975 and a London MS for a thesis on mastalgia in 1988. He spent a year at the University of Texas Health Science Center in 1982–1983. He has been awarded Travelling Fellowships by the National Health Service, the International College of Surgeons, the Surgical Research Society, *The British Journal of Surgery* and the James IV Association of Surgeons – not to mention the Churchill Memorial Fellowship, a Hunterian Professorship, the Patey Prize and the Raven Prize. Almost all of his many publications have concerned diseases of the breast, both benign and malignant. Professor Mansel joined the Council of The British Journal of Surgery Society in 1991.

**Representative
of the Association of Surgeons**

PROFESSOR MICHAEL HORROCKS



Michael Horrocks was born in 1947 and educated at Guy's Hospital Medical School, qualifying in 1970. For the next 7 years he worked in clinical posts in and around London, followed by 2 years as a research fellow at King's College Hospital. He obtained FRCS (England) in 1974 and then MS (London) in 1982. Mike Horrocks moved to Bristol as senior registrar in 1979 and was appointed to the consultant staff of the Bristol Royal Infirmary in 1982. In January 1992 he became the first Professor of Surgery in the University of Bath. He is a vascular surgeon and all of his many publications and presentations are in this field. He has particular interests in non-invasive vascular imaging, aneurysm surgery and femorodistal bypass grafts. He serves on the Council of the Association of Surgeons and on the Specialist Advisory Committee in General Surgery. Professor Horrocks joined the Editorial Board of *The British Journal of Surgery* in 1988 and the Editorial Committee (and Council of the BJS Society) earlier this year, taking over from Professor Irving Taylor as representative of the Association of Surgeons.

Robin Williamson

Treatment of asymptomatic popliteal aneurysm: protection at a price

Popliteal aneurysm is the most frequently encountered peripheral artery aneurysm, with an incidence second only to that of the abdominal aorta. More common in men, popliteal aneurysms are frequently bilateral (38-58 per cent of cases) and often associated with proximal aneurysms (32 per cent). Atherosclerosis is the most common aetiological factor but the condition may also be secondary to popliteal artery entrapment syndrome, collagen disorders, infection and blunt or penetrating trauma. The prevalence is not known but symptomatic popliteal aneurysm accounts for one in 5000 general hospital admissions, with one popliteal aneurysm seen for every 15 abdominal aortic aneurysms. Thus, a hospital serving 200 000 people can expect to admit 25 patients with abdominal aortic aneurysm each year, but only one or two with popliteal aneurysm. Symptomatic popliteal aneurysm is a rare emergency but carries a significant risk to the limb; thromboembolic complications occur in 42-77 per cent of cases in surgical series and amputations are reported in 16-20 per cent of patients¹. Surgeons may feel obliged to operate on all detected aneurysms to eliminate these risks, especially in a patient who presents with complications from a popliteal aneurysm and has an asymptomatic aneurysm in the other leg.

Diagnosis is principally clinical but requires a high degree of suspicion. In one series, even symptomatic aneurysms were diagnosed by the general practitioner in only 26 per cent of cases, although 94 per cent were readily palpable². Ultrasonography may be used to determine the size of the aneurysm (which does not correlate with the risk of thrombosis) and also the presence of mural thrombus (which does). Better delineation is obtained using computed tomography or magnetic resonance imaging. Arteriography may mislead by showing only the lumen of the aneurysm, but is important in identifying patency or occlusion in the distal vascular tree. As increasing numbers of patients with acute limb ischaemia are treated by thrombolysis, thrombosed popliteal aneurysms are increasingly being identified as the cause; one series reported a causal incidence of 12.5 per cent, with only one in five of these known to be the cause of the ischaemia before thrombolysis³.

The preferred treatment of symptomatic popliteal aneurysm is widely agreed to be surgical. If the aneurysm is acutely thrombosed, this may be preceded by preoperative⁴ or intraoperative thrombolysis and/or thrombectomy. Autologous vein graft bypass gives the best outcome, although moderate results have been reported using Dacron (Du Pont, Stevenage, UK)⁵ and polytetrafluoroethylene⁶. If a suitable length of vein is not available, the use of an anastomotic vein cuff or patch may improve a prosthetic graft. The immediate results of surgery are good but crucially dependent on the patency of the distal vascular tree. Distal pulse recovery is associated with good long-term patency but not all patients are asymptomatic after arterial reconstruction and further aneurysms may develop⁷.

The treatment of asymptomatic popliteal aneurysm poses a different problem. There are no controlled studies of conservative management, nor is the natural history of the condition in the general population known. Prophylactic surgery may prevent the development of distal occlusions but remains controversial. Early operation is often recommended from the evidence of complications in historical surgical series. Even recently published studies^{1,7} from busy centres may contain patients from the late 1950s, because the condition is uncommon and large numbers can be accumulated only over decades. Some reports draw conclusions weighted by inclusion of asymptomatic aneurysms in limbs contralateral to symptomatic aneurysms. There is no doubt that operating before complications have occurred is generally straightforward and yields good results, whereas after the onset of complications the outcome is less favourable. However, it is likely that surgical series will overstate the probability of complications in the asymptomatic population. It is claimed⁷ that complications occur in 29 per cent of patients with asymptomatic popliteal aneurysm followed for at least 40 months and others⁶ have reported the development of ischaemic complications in five of 14 asymptomatic patients observed for 26 months. It is also stated⁷ that the probability of complication rises from 24 per cent at 1 year

to 74 per cent at 5 years, but these grave predictions contain the bias of surgical series and the reduced life expectancy of affected patients should not be forgotten. Of the 12 patients in this series who developed complications, only four required surgical intervention and few survived long enough to experience trouble from their aneurysm⁷. Life expectancy for those with a popliteal aneurysm is approximately half of that of a matched population, with more than half of those affected dying within 5 years of diagnosis and only 35 per cent surviving for a decade. If multiple aneurysms are present, the latter figure is reduced to 16 per cent. More than half the patients have significant hypertension and others have coronary artery disease or diabetes; the average operative mortality rate⁸ may exceed 10 per cent.

In favour of conservative management, it has recently been shown⁹ that aneurysms asymptomatic at the time of presentation may remain so over several years, in contrast to those in patients who are asymptomatic initially but who are treated surgically and become symptomatic. Successful bypass does not necessarily prevent further problems, particularly if the distal vessels are obstructed or there are proximal aneurysms. An actuarial graft patency rate at 4 years of between 30 and 92 per cent has been reported, depending on the patency of distal vessels. Late failure may be 'the consequence of a complication of a more proximal reconstruction'⁶. The close anatomical relationships of the popliteal vein and sciatic nerve branches expose these structures to damage during surgery and there is a significant risk of deep venous thrombosis and foot drop respectively¹⁰. Operation for the asymptomatic aneurysm can offer protection from possible future hazards, but only at a price.

The availability of safe thrombolysis now bears upon the surgical dilemma of the asymptomatic patient¹¹. It may allow unnecessary surgery to be avoided in that majority of patients who present with small aneurysms containing little clot; these lesions rarely cause complications and may be managed by observation in much the same way as the small, non-tender abdominal aortic aneurysm. Any sudden, unexpected thrombosis usually responds to preoperative or intraoperative thrombolysis, which prepares the leg for surgical bypass. The natural history of popliteal aneurysm needs to be clarified by screening and a longitudinal prospective study, but this will take time and large numbers of patients. Until then, a pragmatic approach relying on thrombolysis should both reduce the number of unnecessary operations and improve the outlook for those patients in whom ischaemic limb complications have put the need for intervention beyond doubt. As yet, there is insufficient scientific evidence for widespread prophylactic surgery on either medical or economic grounds.

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Anorectal reconstruction

Colorectal surgery has progressed significantly over the past few decades. Restoration of quality of life has been at the forefront of the surgeon's mind; sphincter preservation has supplanted sphincter excision when planning a surgical procedure for low rectal cancer, ulcerative colitis or familial adenomatous polyposis. A greater appreciation of anorectal physiology and the widespread use of stapling devices have resulted in a significant decrease in the formation of permanent stomas. Despite these advances, there remain patients who, because of the nature of their disease or for technical reasons, require excision of the anorectum and sphincter apparatus. Others who suffer from anorectal agenesis never achieve normal function, despite pull-through procedures. It is for these groups that some surgeons have attempted reconstruction of the anorectal region in the hope of re-establishing gastrointestinal continuity and continence.

There is usually no practical difficulty in re-establishing gastrointestinal continuity; the colon, or indeed the ileum, can invariably be mobilized to reach the perineum. Rather, it is the development of a neocontinence mechanism that has been the problem. This relies on developing a barrier to the egress of neorectal contents that is pliable enough to allow evacuation to occur. A variety of techniques have been tried, most of which rely on the transposition of skeletal muscle to replace the sphincter mechanism. The adductor longus¹, gluteus maximus² and obturator internus³ muscles have all been used for neosphincter construction, but it is the gracilis which has received most attention. This muscle has been used to augment a deficient external anal sphincter in patients who were incontinent but had an intact anorectum. Simonsen *et al.*⁴, however, used the gracilis as a neosphincter after rectal excision and coloanal anastomosis in patients with rectal cancer. Despite their apparent success – 17 of 22 cases were described as having excellent or good continence – most surgeons in this field have remained sceptical. One group has therefore modified Simonsen's procedure by detaching and reattaching the origin of the muscle to the pubic arch, so as to alter the direction of contraction and make closure of the neoanal canal more efficient⁵. Another variation has been to use both gracilis muscles – one to replace the puborectalis muscle and the other to replace the external anal sphincter. Cavina and colleagues⁶ have electrically stimulated both muscles intermittently for a few weeks after operation to prevent atrophy.

Most observers believe that any continence that is achieved results from the presence of an adynamic ring of muscle which obstructs defaecation. However, if egress of neorectal contents is prevented during normal activity, voluntary evacuation will of necessity be difficult or impossible. For the gracilis muscle to function as a neosphincter, it must maintain its tone almost indefinitely, yet relax sufficiently for evacuation to occur. Since it is a fast-twitch, fatiguable muscle, it cannot function in this way. Long-term continual electrical stimulation using an implanted, programmable, electrical stimulator can convert the gracilis muscle from a fast-twitch to a slow-twitch, fatigue-resistant muscle, thus imparting to it the essential property of sphincter muscle^{7,8}. Such a technique has recently had some success, both in patients who have undergone coloanal anastomosis after abdominoperineal excision of the rectum, and in those who have remained incontinent after a pull-through procedure for anorectal agenesis. Independent studies in the UK and the Netherlands using similar techniques confirm the feasibility of such an approach^{9,10}.

Are there alternatives to transposition of skeletal muscle to form a neosphincter? Some have used a cuff of colonic circular muscle which was stretched and then wrapped around the distal colon used to form a colostomy¹¹. Although great claims were made for this smooth muscle sphincter, these have not been confirmed and the general opinion is that any continence achieved was induced by the colonic washouts which were required. Recently, the artificial AMS 800 (American Medical Systems, Minneapolis, Minnesota, USA) sphincter, initially devised for urinary incontinence, has been modified and used to replace the anal sphincter in some faecally incontinent patients¹². A silicone rubber cuff surrounds the anal canal and, when inflated from a reservoir, occludes the anal orifice. Only a few patients have been treated, no long-term results have been reported, and it has not yet been used after coloanal anastomosis. However, there must be reservations about this approach: in addition to mechanical problems, such as cuff leakage and valve failure, foreign material

applied sufficiently closely around the colon to exert pressure to occlude its lumen is likely to erode into the lumen eventually. It remains to be seen whether the manufacturers of these devices can overcome such disadvantages.

Creating a dynamic sphincter mechanism is not the only hurdle that needs to be overcome in restoring normal anorectal function. Loss of the rectum removes reservoir capacity and frequent bowel actions may be a consequence. Colonic pouch formation, combined with the electrically stimulated neoanal sphincter, may correct this deficit, although some observers have found that when a pouch is added to a coloanal anastomosis evacuation becomes difficult. Yet another problem to overcome is the loss of sensation which results after total excision of the rectum and anal canal. At present, after total reconstruction patients must evacuate at set intervals to compensate for this sensory loss. However, there is reason to believe that, with time, some may develop neorectal sensation. Although the anal canal with its highly specialized mucosa is lost, some of the receptors which seem to detect rectal fullness are situated in the levator ani muscles and pelvic floor and may be preserved. It is interesting that in one series⁴ the majority of patients who underwent total anorectal excision and coloanal anastomosis eventually experienced some degree of sensation.

Surgeons who deal with rectal cancer and ulcerative colitis must feel confident that their operation eradicates the disease. Patients, however, have the right to expect that, while eradicating the disease, the surgeon will also restore their quality of life as far as possible. In many patients, both aims can be achieved by some form of sphincter-preserving operation. In others, a permanent stoma is required. While many can live a full and active life with a stoma, some find it a tremendous burden and it behoves us to seek alternatives. Anorectal reconstruction with a coloanal or even an ileoperineal anastomosis and some form of neosphincter represents an attempt to do this. Early results with the electrically stimulated gracilis neosphincter are encouraging, but there is a long way to go. At present, patients wishing reconstruction need to be highly motivated as they must undergo several procedures, and continence, although in some degree restored, is not perfect. Defaecation problems may occur, perhaps because of absent sensation, and patients must evacuate at set intervals. Nevertheless, many are eager to undergo these operations despite their imperfections and there is optimism that the problems will soon be overcome.

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Monitoring and cerebral protection during carotid endarterectomy

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Two recently published multicentre trials have confirmed the overall benefit of carotid endarterectomy in symptomatic patients with severe carotid artery disease. The key to improving further the long-term advantages of carotid endarterectomy, however, remains the continued reduction of the initial operative risk. While the principal responsibility for this continues to be borne by the surgeon, specifically in reducing technical error, the time is perhaps approaching when he or she might also be able to apply some of the recent advances in cerebrovascular research to reduce operative morbidity still further in the future. This article summarizes the aetiology and pathophysiology of operation-related neurological deficits and reviews current approaches towards intraoperative monitoring, cerebral protection and assessment of quality control.

'The discussion of ways to prevent neurologic complications cannot be limited to the pros and cons of a temporary shunt.'

Alain Branchereau¹

The European and North American trials have shown that carotid endarterectomy offers a better long-term prognosis than medical therapy in symptomatic patients with a severe (> 70 per cent) stenosis of the internal carotid artery (ICA)^{2,3}. These results have important implications. First, referral practice and investigation will have to change so that appropriate patients can be considered for surgery or medical therapy; it will no longer be acceptable simply to start patients on aspirin without further investigation. Second, operative risks must be reduced, particularly if a greater proportion of higher risk patients are referred. This entails more than just careful patient selection and meticulous technique. Recent advances in knowledge of the pathophysiology of cerebral ischaemia (which often fail to reach the general or vascular surgical literature) have important implications for the development and application of cerebral cytoprotective agents and, by inference, for the attitude of surgeons towards intraoperative monitoring.

Pathophysiology of operation-related neurological deficits

The risk of death and/or major stroke after carotid endarterectomy^{2,3} is 2-4 per cent, although the morbidity rate is significantly higher if all minor neurological deficits are included⁴, possibly increasing to 12 per cent if silent infarcts seen on computed tomography (CT) are considered⁵. Two-thirds of operative strokes occur during surgery, of which 20 per cent are probably haemodynamic in origin⁶. While embolization remains the principal cause of morbidity, a higher proportion of intraoperative strokes are caused by haemodynamic failure than is observed in the natural history of spontaneous stroke, of which perhaps 1-2 per cent arise in this way⁷. Particulate embolization is invariably associated with technical error (Table 1). Air embolization may occur in up to 90 per cent of patients, particularly following shunt insertion

and final restoration of flow^{8,9}, and although its significance remains controversial, it is clearly undesirable and merits further study. Apart from cross-clamping, a haemodynamic stroke may follow a critical reduction in boundary zone perfusion pressure secondary to intracranial occlusive disease or may occur as a consequence of shunt complications (occlusion, kinking, malpositioning, spasm). In the absence of transcranial Doppler ultrasonography (TCD) or other in-line monitoring methods, one might incorrectly attribute any ensuing neurological morbidity to shunt-induced embolism rather than to a haemodynamic cause. After operation strokes tend to be thrombotic, although embolization and intracerebral haemorrhage may also occur. Early thrombosis may affect 2 per cent of patients¹⁰, and may even start during the operation owing to an enhanced rate of platelet deposition^{11,12}. Thrombosis may be associated with technical error such as an arterial kink, intimal corrugation or flap formation, but may also result from a systemic cause such as hypotension or a heparin-mediated platelet membrane antibody¹³.

Certain patients appear to be at higher risk of operative stroke, including those with a history of crescendo transient ischaemic attacks or recent stroke¹⁴, evidence from CT of infarction¹⁵, a residual neurological deficit before operation⁴, and complex ulcerated lesions at the carotid bifurcation^{4,16}. The latter condition has not been well studied. Although embolization by relatively large particles or thrombi is the principal cause of intraoperative stroke, insufficient attention has been paid to the vulnerability of the haemodynamically compromised brain to minor embolization or an apparently innocuous reduction in cerebral perfusion pressure⁴. Impaired cerebral vascular reserve (arterioles with a reduced capacity to vasodilate in response to a declining cerebral blood flow) and cerebral embolization are not mutually exclusive and may explain why certain patients are more at risk during surgery⁴, particularly as it has been shown that the normal brain is better able to withstand periods of ischaemia than is a brain that has previously suffered ischaemic damage¹⁷. In other words, patients with cerebral infarction, a residual neurological deficit, and partial or total haemodynamic compromise are less capable of adapting to reduced perfusion or minor emboli, so the margin for technical error is reduced or possibly non-existent.

Table 1 Factors associated with development of an intraoperative neurological deficit

Embolie	Thrombotic	Haemodynamic
Atheromatous plaque	Perioperative hypotension	Carotid clamping
Carotid dissection or mobilization	Uncorrected internal carotid artery kink or loop	Shunt occlusion or kinking
Shunt insertion	Platelet-fibrin thrombus	Shunt malpositioning or malfunction
Intimal flaps	Idiopathic	Shunt-induced spasm
Clamp induced	Heparin dependent	Intracranial disease or thrombosis
Residual	Wall irregularity	
Shunt induced	Intimal flap	
Incomplete endarterectomy	Hypoplastic internal carotid artery	
Suture stenosis	Perishunt thrombosis	
Distal arteriotomy closure		
Toe of patch angioplasty		
Air embolism		
Shunt insertion		
Inadequate backventing of arteriotomy		

Pathophysiology of cerebral ischaemia

A perfusion of 40–60 ml per 100 g brain per min provides a plentiful supply of oxygen and metabolic substrates for aerobic respiration to maintain high-energy phosphate stores, half of which are used to maintain the sodium–potassium ionic pump¹⁸ and a resting neuronal membrane potential difference¹⁹ of -70 mV. As the pressure gradient across an extracranial carotid stenosis increases, there is first a compensatory increase in cerebral blood volume (in order to maintain cerebral blood flow) followed by an increase in oxygen extraction fraction, before the true haemodynamic reserve is exhausted and cerebral blood flow declines²⁰. Below 12–15 ml per 100 g brain per min the electroencephalogram (EEG) becomes flat or isoelectric and evoked potentials disappear; this perfusion level is termed the flow threshold for failure of neuronal electrical function²¹. Below this level, metabolism switches to anaerobic glycolysis but residual perfusion is still sufficient to maintain near-normal adenosine 5'-triphosphate (ATP) levels²¹, i.e. there exists a narrow range of perfusion (perhaps 5–7 ml per 100 g brain per min) in which there is loss of cerebral electrical activity, but sufficient blood flow to maintain high-energy phosphate stores and hence cell viability. Below 10 ml per 100 g brain per min a complex sequence of events occurs which if not arrested will lead to neuronal death; this perfusion level is termed the flow threshold for failure of energy metabolism and ion pumping²¹. Declining high-energy phosphate stores cause rapid failure of ionic pumps with a net efflux of potassium ions and influx of sodium and chloride ions and water²¹, ultimately causing cellular oedema and anoxic membrane depolarization²². Lactic acid accumulation reduces cellular pH and may cause damage in its own right²³, while the presence of hyperglycaemia at the time of ischaemic injury may increase the ensuing volume of cerebral infarction²⁴.

Within a short time, there is a significant increase in the extracellular concentration of the excitatory neurotransmitter glutamate²⁵ resulting from the combination of depolarization and failure of glutamate reuptake mechanisms²⁶. Moreover, this spreading wave of depolarization can extend into adjacent non-ischaemic tissues and further potentiate the accumulation of glutamate. The combination of membrane depolarization and glutamate accumulation repeatedly activates the *N*-methyl-D-aspartate (NMDA) receptor complex. This receptor complex is linked to an ion channel that controls calcium entry into the cell²⁷ and, once the channel is open, there is a rapid influx of calcium ions. The presence of raised intracellular calcium ion concentrations (augmented by increased calcium release from impaired mitochondria and the endoplasmic reticulum) triggers a cascade of events that culminates in neuronal death from the release of proteases and lipases, free radical and superoxide formation, and the activation of phospholipase A₂, causing

release of arachidonic acid and prostaglandins which predispose towards vasoconstriction and platelet aggregation^{28–30}.

Reducing the operative risk

A commitment to reducing the operative risk should include not only an attempt to ensure adequate perfusion, but should also exploit the recent advances in cerebrovascular and metabolic research and improve quality control through a combination of personal audit, reduction of technical error and careful intraoperative assessment.

General considerations

A heightened awareness of the need for meticulous technique is the key to reducing operative risk because most of the factors associated with operation-related morbidity are secondary to technical error (*Table 1*). Carotid dissection before clamping should be minimal to reduce the risk of embolization; in many centres the carotid bifurcation is not dissected until the distal ICA has been clamped¹. It is essential to leave the endarterectomy surface free of intimal flaps and debris, and this can be made easier by the use of operating loupes or by argon laser radiation³¹ which also welds the endarterectomy endpoints. The arteriotomy site should be carefully backvented and flushed, although one should be aware that preliminary venting up the external carotid artery (before releasing the ICA clamp) may also lead to cerebral embolization via reversed flow in the ipsilateral ophthalmic artery⁸. The toe of the vein patch or the most distal aspect of the arteriotomy is prone to suture-induced stenosis. This can be prevented by the use of interrupted sutures around the apex or using a stent to aid closure. One should also be aware of the potential for kinking and corrugation of the carotid bifurcation and, if necessary, correct for this. The role of the shunt in carotid surgery is controversial, primarily because it has never been clearly proven to be of benefit. Despite its attractive logic, there are a number of negative features which include difficulty of insertion in the small-calibre carotid, problems visualizing the plaque endpoint, risk of atheromatous or air embolism, intimal dissection or plaque elevation, occlusion, malpositioning or malfunction, kinking and perishunt thrombosis. With care, however, all these problems may be avoided and shunt patency can be monitored using TCD⁸.

Surgeons rely on anaesthetists to maintain a stable cardiovascular environment during carotid endarterectomy. General anaesthesia reduces cerebral metabolism and hence oxygen consumption; isoflurane in particular is associated with fewer EEG changes during carotid clamping than halothane³². Most centres advocate a policy of maintaining blood pressure as close to the preoperative level as possible, although this may

be complicated by the hypotensive nature of many anaesthetic agents and barbiturates. Others have recommended a blood pressure approximately 10–20 per cent above normal³³. Intraoperative hypertension (whether therapeutically induced with phenylephrine or catecholamine-driven as with local or regional anaesthesia³⁴) may be associated with a higher risk of myocardial ischaemia³⁵. The benefits of slight to moderate hypertension must be balanced against the cost in terms of morbidity, remembering that in some studies myocardial events have been the leading cause of postoperative death³⁵. The rationale behind maintenance of systemic arterial blood pressure (SABP) is its close relationship to ICA stump pressure and cerebral perfusion pressure, and hence to the delivery of oxygen and glucose to the brain. This is particularly relevant during carotid clamping because cerebral autoregulation may be impaired. ICA stump pressure and cerebral blood flow may be manipulated by increasing SABP³⁶ and this alone may reverse electrophysiological abnormalities associated with carotid clamping³⁷. In patients with unilateral carotid disease, a 3-mmHg increase in SABP (after carotid clamping) produces a 1-mmHg rise in stump pressure, whereas in patients with significant bilateral ICA disease a 7-mmHg increase in SABP is required to raise the stump pressure³⁸ by 1 mmHg. The normally occurring reduction in cerebral perfusion pressure in the boundary zones between the principal vascular territories must also be considered³⁹. These areas become more vulnerable to an intraoperative drop in blood pressure if there are any associated intracerebral occlusions or stenoses, or areas of infarction surrounded by an already compromised penumbra²¹. Moreover, this vulnerability may be aggravated by factors that impair cerebral autoregulation such as the use of volatile anaesthetic agents⁴⁰ and in hypertensive patients (whose autoregulatory curve is shifted to the right) and those with any other condition that may be associated with pial arterial vasodilatation.

Potential role of cerebral protective agents

The traditional approach to the development of ischaemia is early restoration of cerebral blood flow. This is illustrated by the tendency of many surgeons to re-explore the operated ICA to exclude thrombosis as soon as possible after discovering a postoperative neurological deficit. This will not, however, help in the case of focal, intracerebral embolic events, and restoration of blood flow alone may not reverse an ischaemic deficit⁴¹. With advancing knowledge of the pathophysiology of cerebral ischaemia, attention is now being directed towards cytoprotection (in addition to improving blood flow). Advances relate primarily to reversing the effects of calcium ion-induced neurotoxicity, preventing free radical release and avoiding hyperglycaemia. One of the most promising avenues of research is an attempt to intercept the cascade of events mediated by calcium ion influx. This might be achieved by agents that block the NMDA receptor directly, via its linked ion channel, or by calcium antagonists that do not appear to be receptor mediated⁴¹.

There is an increasing body of *in vitro* and *in vivo* evidence that competitive and non-competitive NMDA antagonists may reduce ischaemic neuronal injury following transient global ischaemia (e.g. after a cardiac arrest) and following focal ischaemic events (e.g. embolism)²⁷. Overall, the results for global ischaemia are not as promising as those for focal injuries²⁷ but, as cytoprotection from the latter would be the principal aim in carotid surgery, NMDA antagonists may yet prove promising for intervention or prophylaxis. The apparent discrepancy between global and focal injuries is thought to be because NMDA antagonists may be maximally cytoprotective only in situations where there is still some remaining cellular energy production (e.g. in the ischaemic penumbra), thus enabling some residual capacity for ATP-driven calcium ion extrusion²⁷. The most consistent finding in animal models of focal ischaemia has been a reduction in the ensuing volume of cerebral infarction when NMDA antagonists are administered

before, and even after, the onset of ischaemia²⁷. Other agents currently under assessment are the non-receptor-mediated calcium antagonists, such as flunarizine⁴¹. Although the exact mechanism of action is unknown, evidence suggests that a delay is caused in the onset of anoxia-induced depolarization and that there is a reduction in calcium ion influx⁴¹. Flunarizine has few significant side-effects and because it has already been used in humans for the treatment of vertigo, migraine and epilepsy, may be one of the first agents to be used in controlled trials⁴¹.

Rationale for intraoperative monitoring

A number of monitoring methods were developed and subsequently rejected, usually because they failed to influence neurological morbidity. This problem is highlighted by current attitudes towards the use of a temporary indwelling shunt which is inserted routinely or selectively to maintain adequate cerebral perfusion during carotid clamping. As noted above, there is no convincing evidence that shunting reduces the operative risk. Now that carotid endarterectomy has found an established place, it is clearly time to embark on carefully designed, randomized trials to evaluate the role of the shunt and, more importantly, the correct criteria for its deployment. If a policy of selective shunting is to be employed, the risk–benefit analysis is dependent on restricting the use of the shunt to those patients at risk of critical clamp-induced ischaemia³⁷; reliable methods are required to identify patients who are in the threshold area between electrical and neuronal failure.

Experience suggests that shunting alone is not the answer¹. The design of future trials must now be considered to evaluate the role of glutamate and calcium antagonists, free-radical scavengers and the avoidance of hyperglycaemia in the reduction of operative risk. These agents should not, however, be expected to confer immunity against developing a neurological deficit. Nevertheless, it is possible that some might prevent extension of ischaemia from the central core of infarction (where there is no residual energy production) towards the periphery, where impaired but functionally viable neurones have some capacity for ATP production, and so reduce the extent of the ensuing neurological deficit. Ideally, a safe agent that could be given on the induction of anaesthesia is needed. If this were possible, monitoring might become less necessary, but because some glutamate antagonists may be associated with hypotension⁴² or cognitive impairment⁴³ a rationale for intraoperative monitoring must be developed that allows identification of impending ischaemia which is not resolved by first-line methods (control of blood pressure, shunt insertion).

No single monitoring method is infallible, partly because of the heterogeneity of the causes of cerebral ischaemia, the complex and often unpredictable sequelae of cellular events and the variable location of the ischaemic insult (i.e. lacunar as opposed to cortical). Monitoring is expensive, particularly when technical support is required, but the avoidance of catastrophic complications is so important that proper evaluation of available methods is essential.

Current intraoperative monitoring methods

There are a number of methods for monitoring cerebral function and outcome during carotid endarterectomy (Table 2). A few, notably measurement of jugular venous oxygen saturation or transconjunctival oxygen tension, and supraorbital photoplethysmography, have not been accepted because of their failure to correlate with other monitoring methods and clinical outcome.

Neurological testing in the awake patient

It is generally accepted that neurological testing while the patient is awake (during regional anaesthesia provided by a combination of deep and superficial cervical plexus blockade) is one of the most sensitive monitors of cerebral function⁴⁴.

Table 2 Current intraoperative monitoring methods

Assessment of adequacy of cerebral perfusion during clamping
Neurological testing in the awake patient
Electroencephalography
Somatosensory evoked potentials
Cerebral perfusion measurement
Transcranial Doppler ultrasonography
Internal carotid artery stump pressure
Internal carotid artery backflow
Jugular venous oxygen saturation
Transconjunctival oxygen tension
Supraorbital photoplethysmography
Identification of intraoperative embolization
Transcranial Doppler ultrasonography
Verification of shunt integrity and function
Transcranial Doppler ultrasonography
In-line Doppler ultrasonography flow probes
Assessment of complete endarterectomy
Intraoperative angiography
Intraoperative ultrasonography
Intraoperative angioscopy

Following carotid clamping, up to 21 per cent of patients may develop aphasia, contralateral paresis, changes in mental status or loss of consciousness⁴⁵ which can usually be reversed by raising the blood pressure or insertion of a shunt. The majority develop symptoms within 2 min of clamping⁴⁶ but, because symptoms may occur later at 10–20 min after clamping⁴⁷, the anaesthetist should continue to test the patient throughout the procedure. This form of testing can identify patients at high risk even when sensitive EEG monitoring remains normal⁴⁸, possibly because the ischaemic insult is located within the deeper structures of the brain and internal capsule. Moreover, assessment while awake may be of particular benefit for patients with a previous stroke or infarct as new electrophysiological abnormalities may be difficult to identify when superimposed on pre-existing abnormalities⁴⁹. Despite these many advantages, most surgeons and anaesthetists prefer to use general anaesthesia. The principal problems of operating on the awake patient include a variety of cardiovascular effects, especially hypertension⁴⁵, which increases myocardial oxygen demand and the risk of myocardial infarction. This is particularly relevant in patients with a history of ischaemic heart disease who may represent 57 per cent of the population undergoing carotid surgery⁴⁹. Further problems include patient compliance and discomfort, movement during dissection, and maintenance of the airway; cerebral metabolic requirements are at their greatest during awake testing.

Electroencephalography and evoked potentials

The EEG represents the summation of spontaneous electrical activity arising from postsynaptic potentials (primarily from the superficial layers of the cerebral cortex) which may be excitatory (depolarizing) or inhibitory (hyperpolarizing)¹⁹. The amplitude of the EEG (μV) and power (μV^2) are indicators of the 'amount of EEG activity' present⁵⁰, while the frequency component is reflected as the relative distribution of frequencies (δ , θ , α , β). The rationale for using an EEG is that as perfusion falls below 18 ml per 100 g brain per min there is loss of high-frequency activity and lower amplitude waves⁵⁰, while below 15 ml per 100 g brain per min the EEG becomes isoelectric, i.e. early focal changes appear. The latter is seen in 10–29 per cent of patients after carotid clamping⁵¹ and is assumed to represent a higher risk of developing ischaemia; it warns the anaesthetist that the threshold for loss of electrical activity is approaching. Appropriate intervention may be undertaken to improve the circulation, or a shunt may be inserted. The development of EEG abnormalities does not necessarily represent the presence of a neurological deficit as the threshold for cellular ischaemia is lower, which may explain the discrepancy between the incidence of EEG changes and

neurological deficits during awake testing⁵² and overall operative morbidity rate⁵³. It also explains why reliance on EEG criteria for shunting increases the rate of shunt usage compared with that used during awake testing⁵⁴. There is also no association between extent of change in the EEG and severity of ensuing neurological deficit⁵⁴. More importantly, because the EEG reflects changes principally in the most superficial layers of the cerebral cortex, there may be no apparent EEG abnormality in the presence of significant subcortical or internal capsular ischaemia⁵⁵. Moreover, the EEG may be influenced by diathermy⁵⁴, the type of general anaesthesia used⁵⁶, arterial partial pressure of carbon dioxide (P_{aCO_2}), hypotension⁵⁴ and clinical presentation. Patients with a previous stroke or infarction are significantly more likely to have pre-existing EEG abnormalities, which may make subsequent interpretation of new and subtle changes more difficult¹⁴; such patients are precisely those at highest risk of suffering an intraoperative neurological deficit. Also, vulnerable cerebral tissue in the ischaemic penumbra surrounding an infarct may be electrically silent⁵⁰. As a consequence, accurate interpretation of EEG changes requires highly sensitive multichannel equipment and an experienced technician with access to either a neurophysiologist or neurologist. Because many centres have staffing or financial limitations, and because many consider the EEG to be oversensitive⁵⁵, attention has been directed away from the unprocessed 'raw' EEG (multiple channels displaying voltage as a function of time) to processed EEG systems. Here the raw EEG data are analysed, condensed and presented in a more easily interpreted way by filter processing, power spectrum analysis, period–amplitude analysis and waveform analysis. A number of such systems are now available for evaluation in trials. One uses period–amplitude analysis, which enables zero-crossing rates, integrated amplitude values and interhemispheric asymmetry ratios to be calculated and presented as easily interpreted graphical displays, in association with on-line recording of basic patient data such as blood pressure, drug administration, anaesthetic regimen, etc. Transient interhemispheric asymmetry (responding to manipulation of blood pressure or shunting) has never been associated with an intraoperative stroke but 50 per cent of patients with persisting asymmetry have been shown to develop major neurological morbidity⁵⁷. Such a system could be used in trials of cerebroprotective agents.

The potential value of somatosensory evoked potentials (SEPs) in carotid surgery was first evaluated by Markand *et al.*⁵⁸ in 1984. Unlike the EEG, which is oversensitive to the superficial layers of the cortex, SEPs reflect the integrity of the afferent pathways from the peripheral nerves to the somatosensory cortex, including the internal capsule. Following stimulation of the median nerve at the wrist, an ascending volley of potentials is generated which travels up the afferent sensory nervous system to the somatosensory cortex via the spinal cord and brain stem¹⁹. The SEPs, recorded by scalp electrodes, are time-averaged (the mean of a large number of artefact-free responses) in order that relatively low-voltage potentials can be demonstrated with minimum extraneous noise¹⁹. They are displayed graphically to permit calculation of the central conduction time (the time taken by the afferent stimulus to pass from the dorsal column nuclei to the sensory cortex) and the amplitude of the primary cortical potential. Evidence suggests that these parameters may be better indicators of impending cerebral ischaemia than changes in latency⁵⁹, and that they correlate better with cerebral blood flow⁶⁰ and are perhaps more sensitive than the EEG⁶¹. A number of criteria for shunting have now been advocated, the most common being a 50 per cent reduction in the amplitude of the primary cortical wave and prolongation of the central conduction time by 1 ms. Appropriate use of these criteria⁶² may reduce the rate of shunt usage to about 11 per cent. The principal advantage of SEP monitoring is its ability to evaluate the deeper structures of the brain, but it requires a finite time for data to be acquired, averaged, filtered and displayed. An experienced operator is essential to exclude artefacts, as is access to a neurophysiologist

or neurologist. In common with the EEG, SEPs are affected by a number of anaesthetic, analgesic and sedative drugs and by changes in blood pressure, all of which must be taken into account when interpreting the findings^{19,62}.

Measurement of cerebral perfusion

A few centres have operating table headrests that incorporate external scintillation detectors to enable measurement of cerebral perfusion after carotid clamping using the xenon washout technique¹⁴. This method requires a steady physiological state and is not very practicable. The inert gas washout method is oversensitive to the superficial layers of the cerebral cortex to the exclusion of the deeper regions of the brain; it may ignore ischaemic zones and record emissions from overlying normal tissues⁶³. This may explain the discrepancy between cerebral perfusion and TCD findings⁶⁴, EEG abnormalities⁵⁶, shunt requirements (27 per cent for a critical level of 18 ml per 100 g brain per min)⁶⁵ and neurological outcome⁶⁶. In general, EEG changes are not usually seen with a perfusion in excess of 30 ml per 100 g brain per min, while major changes become apparent below 18 ml per 100 g brain per min; these thresholds may vary with different anaesthetic agents⁶⁵.

Internal carotid artery stump pressure and backflow

The ICA stump pressure is the arterial pressure in the ICA distal to the clamp and represents the contribution of the vertebrasilar and contralateral carotid inflows to the collateral circulation⁶⁷. Its use as an index of the collateral circulation during carotid clamping was proposed by Moore and Hall⁶⁸ in 1969 and a range of thresholds (25–70 mmHg) have been recommended as criteria for shunt insertion. Although a single stump pressure measurement and subjective assessment of ICA backflow are probably the easiest and most accessible methods for assessing collateral flow, they do not reflect subsequent changes in perfusion during the entire period of clamping and may be dangerously misleading in the presence of significant middle cerebral artery (MCA) mainstem disease. Stump pressure is affected by a large number of factors³⁶ including anaesthetic agents, systemic blood pressure, cerebral venous pressure, intracranial pressure, P_{aCO_2} and arterial partial pressure of oxygen; errors of between 5 and 50 mmHg may be present in up to 13 per cent of calculations⁵¹, usually because of problems with instrument calibration. Few authors actually state whether it is the systolic or mean pressure that is being measured. Overall, there is a tendency for a low stump pressure to correlate with an increased operative risk⁶⁹, but one must accept that a reliance on stump pressure criteria will increase the rate of shunt usage⁵¹. There may be an unreliable correlation with EEG data⁷⁰, awake testing⁷¹, cerebral perfusion⁷² and clinical outcome⁷³, particularly in patients with a previous history of stroke⁷⁴. As with all monitoring techniques, however, its benefits must be balanced against its limitations; a high stump pressure will not protect a patient against embolization secondary to technical error.

Transcranial Doppler ultrasonography

By directing a low-frequency ultrasound beam through the relatively thin temporal bone, it is possible to measure blood flow velocity in the basal cerebral arteries⁷⁵. The most important of these (with respect to carotid surgery) is the MCA and by using a fixed-head probe system it is possible to monitor mainstem velocity in this artery continuously throughout the operation⁸. This makes it more practical than cerebral perfusion methods but it is essential to remember that blood flow velocity is not synonymous with absolute blood flow; according to the Hagen–Poiseuille law, the latter is proportional to the fourth power of the vessel radius while velocity is proportional to the radius squared. This might explain some of the apparent discrepancies observed between MCA velocity and cerebral perfusion measurements⁶⁴, particularly as the latter are more sensitive to the superficial regions of the cerebral cortex while

the former perhaps reflects flow to the basal arteries. Thus, because the MCA diameter is unknown, overinterpretation of minor velocity changes should be avoided. In practice, however, provided end-tidal P_{aCO_2} remains stable, it has become conventional to use relative changes in middle cerebral artery velocity (MCAV) as an index of change in associated blood flow⁷⁶.

Preliminary experience with TCD indicates that the technique shows the predictable changes associated with carotid clamping and shunt insertion^{8,9} and that there is a good correlation between MCAV and ICA stump pressure⁸. A systolic ICA stump pressure of 50 mmHg corresponds to a peak velocity of 42 cm s⁻¹ and a mean velocity⁸ of 30 cm s⁻¹. Few studies have correlated TCD with the EEG and SEP. These should be undertaken but it is inevitable that discrepancies will occur as the EEG and SEP reflect the functional state of the brain while TCD measures some parameter of blood flow. The introduction of TCD, however, often heightens awareness of potentially dangerous occurrences during carotid endarterectomy. These include excessive manipulation of the carotid bifurcation (as manifest by its resultant effect on the MCA waveform)⁸, shunt kinking and malfunction⁸, and air or particulate embolization (differentiation is at present not possible with TCD)^{8,9,77}. TCD may also be helpful in differentiating between intraoperative haemodynamic or embolic neurological events^{8,77} and can usually diagnose postoperative ICA thrombosis on the basis of directional flow changes in the circle of Willis. Overall, TCD shows considerable promise as a monitoring and quality-control technique, but is most likely to find its optimal role in conjunction with an electrophysiological method such as EEG or SEP measurement.

Intraoperative assessment of carotid endarterectomy

It is perhaps surprising, given the fact that the integrity of many other types of vascular reconstruction is verified by some form of on-table assessment, that similar consideration is so seldom applied to carotid endarterectomy. This is despite the fact that technical error is the most significant contributor to operation-related morbidity, that the resultant effect may be catastrophic in severity, and that the 'time window' for intervention is probably very small⁷⁸. Perhaps some surgeons are reluctant to concede that, despite their very best efforts, some technical error may have escaped their attention. However, significant intraluminal abnormalities may be present that are not evident to either inspection or palpation⁷⁸. In 1967, Blaisdell *et al.*¹¹ demonstrated that up to 26 per cent of patients may have a technically unsatisfactory result following endarterectomy, including a 5 per cent on-table ICA occlusion rate. This experience has subsequently been verified by others using on-table angiography⁷⁹, ultrasonography (pulsed Doppler and spectral analysis⁷⁸, B-mode imaging⁸⁰, duplex⁸¹ or continuous wave⁸²) and occasionally angiography⁸³. Angiography is limited by the need for clear biplanar views or fluoroscopic screening, while most duplex probes are too large to image the upper limit of the endarterectomy. However, using angiographic criteria of residual stenosis >30 per cent, intimal flap >3 mm, kinking or occlusion⁸⁴, or flow disturbance detected by analysis of the back-scattered Doppler signal⁷⁹, 2–10 per cent of endarterectomy sites require re-exploration^{79–81,84}. Unfortunately, on their own neither angiography nor ultrasonography is at present reliably accurate⁸⁰; there is perhaps a tendency to screen with ultrasonography and to proceed to angiography when there are abnormal findings. In general, however, a normal laminar flow pattern or mild flow disturbance correlates with normal angiography⁷⁹. Evidence suggests that a policy of intraoperative assessment helps surgeons to improve their operative technique⁸⁵ and may start to reduce the incidence of operation-related morbidity⁸⁰.

Conclusion

Carotid endarterectomy now has a justified place in the management of symptomatic cerebrovascular disease. However,

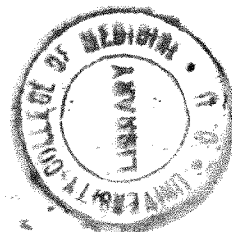
despite almost 40 years of experience (and more than 1 000 000 endarterectomies) certain questions still require answers. Monitoring equipment and technical staff are very expensive and, while many of the techniques are clinically useful, none has proven to be clearly superior. But there are grounds for optimism. A commitment to meticulous operative technique must be renewed which, with quality control and close collaboration with neurological, neurophysiological and research colleagues, should lead to safer surgery for patients in the years to come.

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Subtotal splenectomy in Gaucher's disease: towards a definition of critical splenic mass

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Partial splenectomy is currently the favoured surgical approach for Gaucher's disease. Preservation of splenic tissue is indicated to prevent susceptibility to overwhelming postsplenectomy sepsis, to delay the massive deposition of glucocerebroside in the liver and bones, and to relieve symptoms of hypersplenism. Controversial issues and technical problems related to partial splenectomy for Gaucher's disease are discussed and a definition of critical splenic mass considered.

Gaucher's disease is an autosomal recessive genetic disorder of sphingolipid metabolism. A deficiency of β -glucocerebrosidase causes an accumulation of glucocerebroside in the reticulo-endothelial system and bone marrow. The surgical implications of this storage disease are related to the massive spleromegaly and hypersplenism that usually develop, in either early childhood or adolescence. Following splenectomy, which was the traditional treatment for affected patients, an increase of glucocerebroside deposition is observed in the liver and bones. However, these patients also have a higher than usual risk of fatal overwhelming postsplenectomy sepsis (OPSS), which in early childhood may increase by a factor¹ of up to 300.

Since the preservation of splenic tissue is presumed to prevent, or at least retard, this complication, partial splenectomy is currently the favoured surgical approach. Nevertheless, there is no general agreement about the minimum splenic mass that should be preserved for the best results. Although the literature records no patient who underwent partial splenectomy as dying from OPSS², Rodgers and colleagues stated in 1987 that partial splenectomy for Gaucher's disease 'must be considered an unproven surgical procedure at this time' because long-term follow-up is not yet available and early recurrent splenomegaly and hypersplenism not uncommon³. The aim of this review is to consider some contentious issues related to partial splenectomy and to highlight some of the relevant dilemmas and technical problems.

How much spleen to remove or how much to leave

The term 'partial splenectomy'⁴⁻⁹ is not only inappropriate but deceptive. From the beginning the term was meant to indicate resection of 80 to 85 per cent of the spleen and the term 'subtotal splenectomy' used by Guzzetta *et al.*^{10,11} is, therefore, more accurate. Some surgeons² have recommended removal of an even greater proportion, 90 to 95 per cent, for which the term 'near-total splenectomy' would be more appropriate.

To anyone who has undertaken or observed resection of a voluminous spleen often weighing several kilograms and occupying more than half of the abdominal cavity, it is clear that in the course of the operation it is very difficult to assess or measure separation of 80, 85 or 90 per cent of the organ. A review of cases described in the literature has indicated that in many only two-thirds of the spleen was removed⁷. Moreover, from a review of published radiological findings and isotope scans of splenic remnants, it is clear that the remaining splenic mass is often much larger than that of a normal spleen. For example, if a 7-year-old child weighing 25 kg has a spleen weighing 2.5 kg (10 per cent of body-weight) and 85 per cent is removed, a remnant weighing 375 g is left, five times the weight of the normal spleen at this age¹². Fleshner *et al.*⁸

described an infant aged 18 months from whom they removed 710 g of splenic tissue, estimated to be 85 per cent of the total spleen. Calculation shows that the remnant weighed about 125 g, whereas a normal spleen at this age¹² weighs 30 g.

The entire approach of estimating the percentage of spleen resected appears to be misguided. What should be being discussed is not how much should be removed, but how much spleen is to be left. There have been numerous studies carried out in experimental animals on the subject of the minimal splenic remnant necessary for preservation of immune capacity^{4,13-15}, but there are no valid data from humans. Constantopoulos *et al.*¹⁶ described a circulating tetrapeptide (tuftsin) that stimulates phagocytosis by direct action on leucocytes. Tuftsin activity is lost 6 to 8 weeks after splenectomy. It has been reported that following splenectomy for crushed spleen, the organ was 'reborn' in 50 to 66 per cent of patients by implantation of tissue fragments scattered over the surface of the peritoneal cavity¹⁷⁻¹⁹. However, the amount of splenic tissue that develops in such cases of spontaneous splenosis is relatively small and does not have the immunological value of a splenic remnant with its own blood supply⁴. Moore *et al.*²⁰ reported a case of OPSS following autotransplantation of splenic fragments in a pocket created in the omentum. Likhite²¹ and Livingston *et al.*²², however, found that implanted splenic fragments promoted the formation of antibodies by lymphocytes, as well as the formation of specific opsonins and tuftsin. Evidently, the titre of these opsonins and antibodies is not of proven value against sepsis or of sufficient efficacy in filtration of particles and removal of pneumococci from the blood^{4,13,15,19}. The only proven immunological role that is regained after reimplantation is the restoration of total circulating immunoglobulin M; splenectomy is frequently associated with a reduction in blood concentrations of this antibody and normal levels have been reported in patients with a regenerated spleen²³⁻²⁵.

The presence of an intact vascular supply and normal splenic microvascular architecture appear to be crucial in obtaining the greatest beneficial effect from the residual organ^{14,26}. For these reasons, hemisplenectomy has been found to be superior to autotransplantation when comparing blood clearance and survival^{14,27,28}. It would appear from most studies in animals that one-third of a normal spleen is sufficient to preserve normal immunological function, including filtration and removal of pneumococci from the blood^{9,29-31}. This fraction is therefore considered to be the 'critical splenic mass'³⁰. It must be stressed, however, that this refers to a healthy spleen with a good normal physiological blood supply and with good regenerative potential⁴; in Gaucher's disease the tissue is pathological.

Most of the splenic enlargement in Gaucher's disease, during both primary growth and regeneration following partial

splenectomy, is caused by deposits of glucocerebroside and proliferation of Gaucher's cells. It is unknown to what extent the active reticuloendothelial system can regenerate and proliferate. However, by leaving 10 to 15 per cent of the pathological spleen, a remnant that is usually larger than an entire normal spleen, sufficient functional tissue for defence against OPSS is preserved, as shown by the absence of such sepsis following partial splenectomy in these cases^{2,7,9,32}, even though the function of the remnant is impaired. This brings us back to the question: What is the minimal amount of splenic tissue necessary in *Gaucher's disease* to ensure its immunological function, while delaying rapid organ regeneration for as long as possible? The answer is yet to be found.

In practice, the amount of spleen left is not determined by an ideal estimated size but through technical necessity (i.e. the blood supply). This differs from patient to patient and is affected by the presence of infarcts. Guzzetta *et al.*¹⁰, who recently reported the largest series of partial splenectomy for a variety of aetiologies (33 cases), admit that they tried not to leave a remnant larger than $5 \times 8 \times 8$ cm, that is a volume of 320 cm³ or at least twice the size of the normal adult spleen. There is no doubt that in Gaucher's disease one must aim for a smaller splenic remnant. The normal spleen¹² at age 18 months weighs about 30 g, at age 6 years about 60 g and at age 11 years about 90 g. Roughly speaking, the remnant should be about the size of the operated child's fist, not the surgeon's fist.

Rate of growth and regeneration of the spleen following partial or subtotal splenectomy

Clinical estimation of the size of the spleen, usually obtained by measuring its spread in centimetres or number of fingers below the costal margin, is devoid of all practical value and does not relate well to the actual size, volume or weight of the organ. Even in healthy children the structure of the chest wall and the costal margin, the height of the diaphragm, and the configuration of the abdominal cavity differ between individuals. In Gaucher's disease the structure of the abdominal cavity and chest wall are affected by the development of hepatosplenomegaly, which causes marked variations in the shape and contents of the upper abdomen. Splenomegaly is most frequently manifested as a downward enlargement, but extension may also occur in other directions and to varying degrees. The distorted configuration of the spleen may differ not only in its three dimensions, but also in its consistency, number of fibrotic scars, and density of Gaucher's cells, leucocytes and cells of the still active reticuloendothelial system. All of these affect the specific gravity and total weight of the organ. Obviously, estimation of size on the basis of spread below the costal arc is limited to comparisons in repeated examinations of an individual child.

Enlargement of the spleen in Gaucher's disease is usually, but not always, gradual and a sudden increase may indicate secondary infection or the development of malignancy³². Size increase results mainly from deposition of glucocerebroside and proliferation of typical Gaucher's cells, but after partial resection it is possible that there is also a marked degree of regeneration similar to that seen in the traumatically damaged spleen^{2,8,9,13,32,33}. Therefore, secondary hypersplenism may develop following successful primary partial splenectomy^{8,34}.

The rate of re-enlargement following partial or subtotal splenectomy cannot be predicted. Reported follow-up is still too short for valid conclusions to be drawn, but it would appear that the younger the child at the time of operation, the more rapid the regeneration³². On the other hand, it is reasonable to assume that those children who required operation at an early age are also those suffering from a more severe form of disease, with rapid splenic enlargement; the 'adult' type of disease is more moderate. This relation to age is illustrated by the 18-month-old child reported by Fleshner *et al.*⁸, who is the youngest so far reported to have undergone removal of approximately 85 per cent of the spleen. Within only 3 months,

rapid enlargement of the remnant necessitated total splenectomy. Additional cases of rapid re-enlargement have been described^{6,9,34,35}.

Does preservation of the smallest possible remnant at the initial operation ensure relatively delayed recurrence of hypersplenism, or is it the natural biological course of the disease that determines the interval before re-enlargement? It is reasonable to assume that the latter is the case, although the size of the splenic remnant after operation must have some effect; every effort should be made to leave no more splenic tissue than that of a normal-sized spleen, according to age³, as already discussed.

Optimal age for initial and subsequent operation

The considerations so far discussed suggest that both the initial and any subsequent operation should be performed as late as possible, providing that early manifestations of hypersplenism such as significant leucopenia and thrombocytopenia do not necessitate early intervention. This doctrine may need to be modified on occasion to account for mechanical disturbances caused by the disease, which lead to growth retardation. This may invite taking benefit from the anticipated growth spurt following earlier splenectomy. Such growth is possible after both partial and total splenectomy, and should be achieved at the optimal time. The delayed closure of the epiphyses in youngsters with Gaucher's disease, which can be documented by radiographs for bone age, must be taken into account. This delayed closure permits relatively late growth. There is, therefore, no strict algorithm available to act as a guide to the best criteria for operation. Each case must be judged carefully, weighing expected benefit against possible deleterious risks.

Expected benefits and shortcomings of subtotal splenectomy

Preservation of a splenic remnant seeks to achieve the following benefits:

1. Prevention of the effects of hypersplenism.
2. A decrease in the risk of overwhelming sepsis.
3. Relief of abdominal discomfort.
4. Improvement in the rate of growth or prevention of growth retardation.
5. Delay in deposition of glucocerebroside in the liver and bones.

The regeneration of the splenic remnant, which may reach huge dimensions within a few years, may be followed by secondary hypersplenism and abdominal symptoms related to the voluminous mass. Although regeneration seems certain, insufficient follow-up data are available to conclude that a second procedure will be inevitable; only further research and prolonged follow-up will provide the answer.

In conclusion, it seems at present that subtotal splenectomy should be considered as a temporary but reasonably satisfactory solution in Gaucher's disease. It is hoped that the results of this relatively new approach will improve with time and with accumulation of further experience.

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Chest physiotherapy for the surgical patient

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This article reviews the evidence that chest physiotherapy is effective in the prevention and treatment of pulmonary complications after major abdominal and thoracic surgery. There is some evidence that regular chest physiotherapy significantly decreases the incidence of pulmonary complications, although the mechanism of this effect is uncertain. It is not known whether chest physiotherapy is effective in the treatment of postoperative pulmonary complications after they have developed.

Chest physiotherapy is frequently used in the prevention and treatment of postoperative pulmonary complications such as sputum retention, atelectasis, pneumonia and broncho-pulmonary infection. Although the incidence of pulmonary complications is higher after upper abdominal or thoracic surgery than after operations on other parts of the body, the relative contributions of other factors such as diaphragmatic dysfunction, pain, the absence of periodic deep breaths and altered pulmonary and chest wall compliance remain unknown.

The duration and frequency of chest physiotherapy for surgical patients is variable, depending on individual requirements, therapist preference and, to some extent, institutional practice. For some patients, one or two treatments will be deemed sufficient, whereas with others frequent or ongoing therapy for a period of days or even weeks may be provided. In addition to physiotherapy, nursing, medical, laboratory, pharmaceutical and radiological resources are employed in the diagnosis and treatment of postoperative pulmonary complications. Given the number of surgical procedures performed, the frequency of pulmonary complications and the high cost of healthcare resources, there are obvious economic and other implications in the appropriate selection of patients and application of chest physiotherapy techniques.

Chest physiotherapy may include preoperative assessment and instruction. After operation, treatment usually consists of at least some form of breathing exercises and coughing. In addition, techniques such as postural drainage, percussion or vibrations to the chest wall, and methods such as incentive spirometry, intermittent positive-pressure breathing (IPPB) and continuous positive airway pressure (CPAP) may be incorporated.

The rationale for employing breathing exercises or devices that encourage deep breathing after operation is that normal or improved respiratory patterns will be promoted, thus improving the distribution of ventilation. The use of postural drainage, percussion, vibrations and coughing is believed to enhance the clearance of excessive or retained pulmonary secretions from the conducting airways, thus preventing or reversing areas of atelectasis and decreasing the incidence of lung infection. If these aims are achieved, it should be possible to document enhanced ventilatory function and pulmonary gas exchange, and to demonstrate that the incidence of pulmonary complications is decreased, the rate of postoperative recovery increased and the clinical course of postoperative pulmonary complications improved.

This paper reviews the evidence that chest physiotherapy for surgical patients is beneficial. Three specific questions are addressed: Does chest physiotherapy enhance clearance of pulmonary secretions and improve pulmonary function after surgery? Does such physiotherapy decrease the incidence of postoperative pulmonary complications? Does chest physio-

therapy increase the rate of recovery or alter the clinical course of pulmonary complications?

As major abdominal and thoracic operations are associated with the most severe impairment of pulmonary function, chest physiotherapy is commonly used in the treatment of these patients. This review is therefore limited to physiotherapy after these types of operation. Because of progress made in surgery and anaesthesia, only articles published in the past 20 years are considered. Although this may have resulted in some important data being overlooked, it seems difficult to draw firm conclusions on the efficacy of chest physiotherapy in the 1990s from results obtained in the 1960s or earlier. This review does not consider pulmonary complications in paediatric patients.

Clearance of pulmonary secretions and improvement of postoperative pulmonary function

Mucociliary clearance is believed to be adversely affected after surgery by the effects of general anaesthesia, intubation and the use of pharmacological agents such as narcotic analgesia in the perioperative period¹⁻⁴. Clearance is further depressed by a reduced ability to cough effectively because of incisional pain and mechanical disruption of the major expiratory muscles. Coupled with decreased regional ventilation, these factors predispose towards potential retention of pulmonary secretions. Although clinicians frequently employ some form of chest physiotherapy after operation and most believe that it helps to clear pulmonary secretions, there have been no studies that scientifically validate this belief. Furthermore, the relative contribution of the individual components of chest physiotherapy has not been investigated.

Only one study has measured the distribution of ventilation after operation⁵. Using fluorodensitometry, pulmonary ventilation appeared to shift from lower towards upper zones after upper abdominal surgery. This was thought to be caused partially by diaphragmatic dysfunction, which has also been documented in other studies⁵⁻⁹.

No study has directly measured the effect of generalized or localized (e.g. abdominal and lateral basal) breathing exercises or other treatments on the distribution of ventilation, although Tahir *et al.*⁵ found that, during deep breathing, 'ventilation tended to be distributed more evenly between upper and lower zones'. It is not apparent whether improvements in ventilation distribution translate into improved gas exchange.

Two studies indirectly measured the effect of breathing manoeuvres on the distribution of ventilation in eight women after cholecystectomy, by measuring the relative contribution of the thoracic and abdominal compartments using respiratory inductive plethysmography^{8,9}. Although diaphragmatic breathing resulted in a relative increase in the excursion of the abdomen, it was not certain whether this was an index of diaphragmatic movement or reflected regional ventilation to

the lower lung fields. Furthermore, as the increases in abdominal excursion were modest, it is unclear whether they were of sufficient magnitude to improve regional ventilation to a clinically useful degree.

Pulmonary function in terms of spirometric values has been extensively investigated. It has been consistently shown that major abdominal or thoracic surgery produces a restrictive pattern of ventilation, manifested by significant decrements in vital capacity and functional residual capacity. These abnormalities generally show gradual improvement over a period of 10–14 days, although the exact duration of the impairment is not known¹⁰.

Four investigations following cardiac or abdominal surgery measured pulmonary function before and after one chest physiotherapy treatment^{11–14}. Treatments included incentive spirometry, IPPB, CPAP and the use of blow bottles. Although spirometric parameters such as vital capacity and functional residual capacity were significantly improved following treatment, arterial blood gases did not change significantly except in one report in which there was a significant fall in the arterial partial pressure of oxygen (P_{aO_2}) 10 min after treatment with IPPB¹². As pulmonary function was usually measured soon after treatment, the duration of any improvement was not certain, although functional residual capacity returned to pretreatment levels at 10 min after treatment in one study¹⁴.

Several workers have investigated the effect of different treatment regimens on the recovery of pulmonary function over a number of days^{15–23}. However, only one of these studies included a true control group that received no specific respiratory therapy²¹. These authors randomized 40 adults at low risk of developing complications following elective cholecystectomy to a control or treatment group that received incentive spirometry at regular intervals. No significant difference was found between the groups in forced vital capacity, forced expiratory volume in 1 s, or arterial blood gases, measured at 2 and 4 days after operation.

Most studies investigating the rate of recovery of pulmonary function have randomized patients to two or more treatment groups^{15–20, 22, 23}. All found pulmonary function to be significantly decreased after abdominal or cardiac surgery. Two studies found that CPAP was significantly better than breathing and coughing exercises and incentive spirometry in the rate of improvement of some (but not all) measurements of pulmonary function after upper abdominal surgery^{19, 20}. One report of patients after cholecystectomy found that those who received IPPB had a significantly reduced vital capacity compared with those undergoing breathing and coughing exercises¹⁷. Other spirometric measurements and arterial blood gases were not significantly different between the two treatment groups. In all other studies, regimens that involved regular treatment with breathing and coughing exercises, incentive spirometry, IPPB or CPAP were not significantly different in their effect on the recovery of spirometric parameters or arterial blood gases measured over a period of days^{15, 16, 18, 22, 23}.

Another aspect of care that could be considered as an adjunct to chest physiotherapy is the use of positioning and early mobilization. Two investigations of patients after upper abdominal surgery found that functional residual capacity improved with the patient sitting compared with the supine position^{24, 25}. Sitting with the bedhead raised 45° was associated with a small but significant decrease in P_{aO_2} compared with the supine position for 19 adults after abdominal surgery²⁶. The arterial partial pressure of carbon dioxide (P_{aCO_2}) also showed a small but significant decrease in the sitting compared with the supine position.

Scheidegger *et al.*²⁷ compared the effect of early *versus* late mobilization on pulmonary function in 51 patients after abdominal surgery. Although patients who began walking on the day of operation had better pulmonary function than those who did not, the patients were not randomized to late mobilization, but were included in this group because surgical or medical reasons prevented early mobilization. Thus it is possible that the two groups were not comparable.

In summary, there has been little conclusive research into the ability of chest physiotherapy to achieve its primary aims of improving the distribution of ventilation and increasing clearance of secretions in surgical patients. The relative contributions of various treatment regimens remain unknown. In particular, the role of techniques such as postural drainage, percussion and vibrations has not been investigated. Although there is some evidence that spirometric parameters are improved immediately after chest physiotherapy, the duration of this effect is not certain and may be transient. There is no clear evidence that any one regimen improves the recovery of pulmonary function over a period of days after surgery significantly more quickly than any other, or indeed above that which occurs spontaneously. The effect of positioning and early mobilization has not been extensively investigated in surgical patients.

Chest physiotherapy and incidence of postoperative pulmonary complications

Although spirometric parameters and arterial blood gases may be adversely affected following surgery, such changes themselves do not necessarily constitute clinically important pulmonary complications. It is important to distinguish patients with self-limiting, clinically unimportant pulmonary complications from those with clinically significant complications that are likely to worsen without specific therapy. Depending on the defining criteria, the incidence of pulmonary complications has been stated to be as low as 3 per cent and as high as 100 per cent after major abdominal or cardiac surgery^{16, 18, 28}.

Clinically important complications are associated with a severe problem of hypoxaemia, radiological and/or auscultatory findings, or sputum changes^{29–33}. In addition, there may be an abnormally raised temperature and white blood cell count (not otherwise explained), and bacterial contamination of sputum. This section reviews only those articles that used these criteria either to define the severity of any changes or to investigate the incidence of what could be considered clinically significant pulmonary complications. A number of reports were excluded as they noted, for example, only auscultatory or radiological changes, without any description of the extent or clinical relevance of these changes^{15, 16, 18–22, 34–45}.

Two studies provide strong evidence to support the role of chest physiotherapy^{31, 46}. These compared the incidence of pulmonary complications in patients randomized to treatment or control groups, the latter receiving no specific respiratory therapy after abdominal surgery. Celli *et al.*³¹ included 81 patients who had undergone upper abdominal surgery. They found that the incidence of pulmonary complications was significantly and dramatically reduced from 88 per cent for the control group to 32, 33 and 30 per cent respectively for patients who received breathing and coughing exercises, incentive spirometry or IPPB at regular intervals. Roukema *et al.*⁴⁶ studied 153 adults considered to be at low risk of developing complications following upper abdominal surgery. They also found the incidence of pulmonary complications of 60 per cent in a control group to be significantly higher than that of 19 per cent in a treatment group which received regular breathing and coughing exercises.

Of the studies that randomized patients to different treatment regimens, two found that incentive spirometry at regular intervals in addition to regular physiotherapy was associated with a significantly lower incidence of pulmonary complications than physiotherapy alone^{30, 47}. However, three other investigations using similar treatment groups found no such effect^{23, 28, 48}, and incentive spirometry alone as a treatment technique was not found to be superior to other treatment techniques, such as IPPB^{12, 31, 33, 49}. When therapeutic regimens such as breathing and coughing exercises, IPPB or positive expiratory pressure were compared, no significant difference was found between treatment groups in the incidence or severity of pulmonary complications^{12, 17, 23, 31, 48–50}. No

studies have been found that evaluated the effect of CPAP on the incidence of clinically significant pulmonary complications.

In conclusion, although there is evidence from two studies that regular chest physiotherapy significantly decreases the incidence of clinically important postoperative pulmonary complications, there is no clear indication of which treatment technique or regimen is superior.

Rate of recovery and clinical course of postoperative pulmonary complications

The effect of different treatment regimens on the rate of recovery after operation has been investigated by measuring pulmonary function over a period of days. These results have been described earlier in this paper. Length of stay in hospital was used as an alternative measurement of recovery in five studies^{22,28,31,33,50}. Celli *et al.*³¹ demonstrated reduced hospitalization for patients who received breathing exercises, incentive spirometry or IPPB, compared with a control group. This was statistically significant only for the incentive spirometry group, however. The other authors found no significant difference in length of stay in hospital between treatment groups that received regular breathing and coughing exercises, incentive spirometry or positive expiratory pressure^{22,28,33,50}.

There is some evidence that physiotherapy is effective in the treatment of acute lobar atelectasis, although this is derived either from single case reports or from studies not restricted to patients after operation⁵¹⁻⁵⁴. No specific investigation was found on the effect of chest physiotherapy on the clinical course of pulmonary complications once they have occurred.

In summary, there has been little research into the effect of chest physiotherapy on the rate of recovery after operation or the clinical course of pulmonary complications.

Discussion

Chest physiotherapy is considered by most clinicians to be an essential part of treatment for patients who have undergone major abdominal or thoracic surgery. Although there is some strong evidence that regular chest physiotherapy significantly and dramatically decreases the incidence of pulmonary complications^{31,46}, the literature does not allow firm conclusions to be drawn on the mechanisms of this effect. It may be that physiotherapy is beneficial as a result of short-lived improvements in pulmonary function¹⁴. If this is shown to be the case in future studies, it will be important to know the duration of any improvements, as this may have implications for the frequency of chest physiotherapy required to achieve the best outcome.

Despite widespread use of treatments like incentive spirometry, IPPB and CPAP, there is surprisingly little evidence to suggest that these are superior to more basic techniques like breathing exercises and coughing. Indeed, there is evidence that IPPB may even have deleterious effects on pulmonary function^{12,17}. Although some of these treatments offer certain advantages over breathing exercises and coughing, in that they require less patient cooperation, all require additional equipment, staffing expertise and expense. Further studies should be undertaken to justify their continued use.

It seems likely that chest physiotherapy, by preventing the retention of pulmonary secretions, may decrease the incidence and severity of certain complications such as atelectasis and bronchopulmonary infection and should improve the course of these. Although clinicians have found chest physiotherapy to be beneficial for many complications, it seems unlikely that it will be found to be effective for pulmonary complications in which retained secretions or decreased regional ventilation are not a characteristic. In medical patients with pulmonary conditions, chest physiotherapy seems to be effective when excessive pulmonary secretions are present, but ineffective when they are not⁵⁵.

Most studies have implicated the decrements in inspiratory ability after operation in the development of pulmonary

complications. Relatively few mention the detrimental effect of surgery on expiratory function, particularly the ability to cough effectively. Although inspiratory ability is of great importance, we believe from our clinical experience that the ability to cough effectively may be of at least equal importance. This hypothesis remains to be tested.

Many of the studies reviewed were of inadequate design or contained only a limited description of methodology, making it difficult to discuss the results with confidence. Some did not randomize patients to treatment groups^{27,45,56}. A number of reports contained general terms, such as 'postoperative' or 'routine' physiotherapy, without further explanation of which procedures or techniques were involved^{22,57-60}. Because of these or similar shortcomings, many papers were not included in this review. A further criticism of some of the papers that were reviewed is the exclusion of patients who were at high risk of developing pulmonary complications^{17,21,23,27,46}. This may have resulted in patient samples that were dissimilar to the types of patient who usually require or receive specific chest physiotherapy in most clinical settings. Only a minority of studies ensured that those performing the measurements were blind to the study^{17-21,23,31,33,47,48,51,54,58,60}. Even more poorly addressed was the issue of observer reliability, with only two reports mentioning this in the study design^{16,54}.

It is evident that there are a number of areas that require further investigation. The following questions could usefully be addressed, particularly for patients at high risk of developing pulmonary complications: Does chest physiotherapy improve the distribution of ventilation and increase clearance of pulmonary secretions? Which physiotherapy techniques are effective in achieving these aims? Can it be confirmed that the regular application of these techniques decreases the incidence of clinically significant complications and speeds recovery? What is the optimal frequency and duration of treatment? Is chest physiotherapy effective in the treatment of postoperative pulmonary complications once they have occurred?

Some may question the need for such studies given the generally accepted and extensive use of chest physiotherapy. We consider, in view of the limited data and lack of clear findings, that they are essential in the delineation and validation of the role of such physiotherapy in surgical patients.

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Editor's announcement

Trocar and cannula

I vividly recall as a medical student being introduced to the equipment called 'a trocar and cannula' which was widely used for drainage of hydroceles, ascites, and other fluid collections. I remember learning that the cannula was the metal tube, and the trocar was the sharp obturator that enabled it to be inserted into the cavity to be drained. There is currently a tendency to confuse and change these definitions, with the use of trocar to mean cannula. In this Journal, we have been guilty of such lack of precision (*Br J Surg* 1992; **79**: 560-1); the matter has been raised elsewhere (*Minimal Invasive Ther* 1992; **1**: 187).

The Oxford English Dictionary gives the definition of a trocar as 'a surgical instrument consisting of perforator or stylet enclosed in a metal tube or cannula'. The word trocar has its roots in the French tongue. The derivation is from *trois* (three) and *carré* (side), describing the triangular form of the tip. The earliest dated reference (1692) in the OED is written *trois-quarts*.

By all means let us continue to use the trocar for laparoscopic surgery. It is an effective instrument that allows easy placement of the cannula through which instruments and telescopes may be passed.

C. D. Johnson
Associate Editor

***In situ* versus reversed femoropopliteal vein grafts: long-term follow-up of a prospective, randomized trial**

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In a prospective, randomized trial, 226 patients undergoing femoropopliteal bypass for lower limb ischaemia were allocated to reversed (123 patients) or in situ (103) techniques. The groups were comparable for age, sex, incidence of diabetes, and indications for surgery. Eleven veins were rejected at operation, nine in the reversed group and two in the in situ group, leaving 114 reversed and 101 in situ grafts for study. Cumulative patency rates were not significantly different between reversed and in situ grafts at any time up to 6 years after operation, with primary patency rates at 1, 3 and 5 years of 84.8, 69.5 and 62.4 per cent for reversed grafts and 79.9, 71.2 and 63.5 per cent for in situ grafts. Small vein grafts (<4 mm in diameter) were associated with patency rates at 1, 3 and 5 years of 63.5, 46.7 and 36.0 per cent compared with 93.9, 82.5 and 75.9 per cent for vein grafts ≥4 mm in diameter ($P < 0.002$, log rank test). The patency rates of small veins employed in situ and reversed were similar. The in situ technique confers neither short- nor long-term advantage over reversed vein grafting for femoropopliteal bypass.

Saphenous vein grafts have been shown to be associated with higher patency rates than synthetic alternatives in femoropopliteal bypass^{1,2}. Controversy remains regarding the optimum method of using such grafts. Proponents of the *in situ* technique claim lower thrombogenicity, better matching for size at the anastomosis, an ability to use smaller veins, and better patency rates³⁻⁸. The validity of these claims remains unproven and their clinical relevance is undetermined.

The long-term results of a prospective, randomized study of *in situ* and reversed femoropopliteal vein grafts is presented, examining which technique confers clinical advantage in the long term.

Patients and methods

From 1983 to 1987, 226 femoropopliteal reconstructions using saphenous vein were randomized, 123 to the reversed technique and 103 to the *in situ* technique. An inadequate saphenous vein (nine in the reversed group and two in the *in situ* group) precluded inclusion in the study in 11 cases. A total of 215 grafts were studied prospectively: 114 reversed and 101 *in situ*.

The indications for surgery were rest pain or necrosis in 122 limbs (61.4 per cent) and severe debilitating claudication in 83 (38.6 per cent). The mean age of the patients was 68.1 years; 23 (10.7 per cent) were diabetic. Twenty-two patients underwent bilateral bypass and an associated inflow procedure was performed in 33 reconstructions (15.3 per cent). The harvested long saphenous vein in the reversed group was kept moist in Hartmann's solution and heparin. *In situ* grafts were prepared by exposure of the whole saphenous vein and ligation of tributaries, followed by stripping of the valve cusps using a Hall's valvulotome.

Operative details of the minimum external vein diameter (measured using calipers), graft length and anastomotic site were recorded.

Follow-up included clinical examination with Doppler assessment of patency and ankle:brachial pressure index measurement. All occlusions were confirmed by digital subtraction angiography or duplex ultrasonography.

Primary cumulative patency curves were constructed by life-table analysis and compared using the log rank test.

Results

The distal anastomosis was to the supragenicular popliteal artery in 129 cases (60.0 per cent: 59 *in situ* and 70 reversed) and to the infragenicular popliteal in 86 (40.0 per cent: 42 *in situ* and 44 reversed). The mean(s.d.) graft length was 39.4(6.4) cm for the *in situ* group and 39.6(8.0) cm in the reversed group.

The *in situ* group had a mean(s.d.) graft diameter of 4.3(0.7) mm and the reversed group one of 4.6(0.9) mm. In all, 138 grafts (64.2 per cent) had a diameter ≥4 mm and 77 (35.8 per cent) a diameter <4 mm. The diameter of the *in situ* grafts was ≥4 mm in 62 cases (61.4 per cent) and <4 mm in

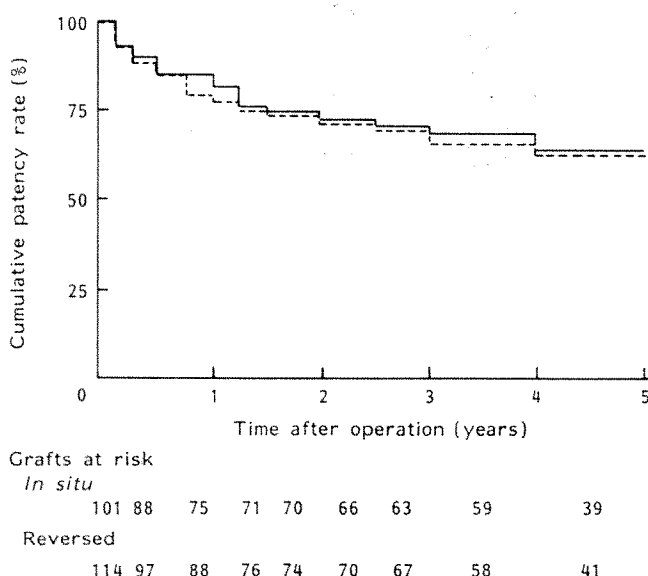


Figure 1 Cumulative patency rates of *in situ* (—) and reversed (---) femoropopliteal vein grafts. There was no significant difference between the two groups at any time after operation (log rank test)

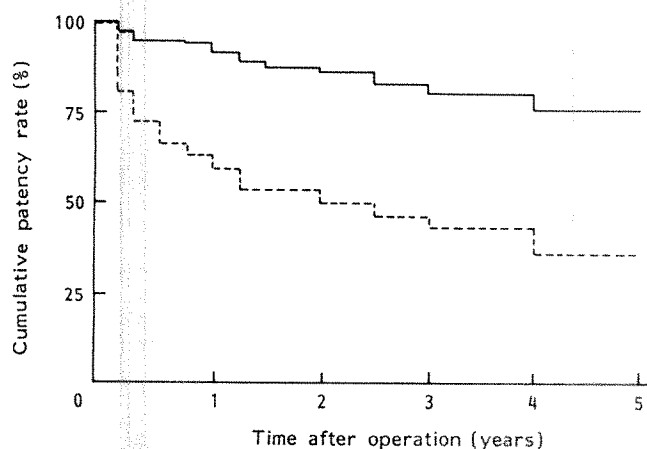


Figure 2 Cumulative patency rates of femoropopliteal vein grafts of ≥ 4 mm (—) and < 4 mm (---) in diameter. Results were poorer for small grafts at all times after operation ($P < 0.002$, log rank test)

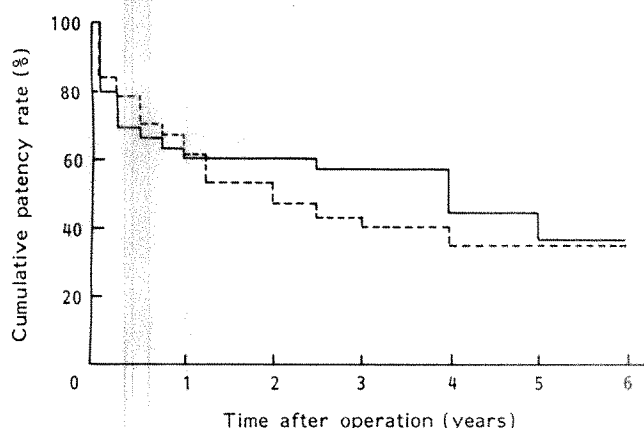


Figure 3 Cumulative patency rates of small (< 4 mm) *in situ* (—) and reversed (---) vein grafts. There was no significant difference up to 5 years after operation (log rank test)

39 (38.6 per cent). For the reversed group, diameter was ≥ 4 mm in 76 cases (66.7 per cent) and < 4 mm in 38 (33.3 per cent).

Inflow procedures were performed in 33 patients: 17 in the *in situ* group and 16 in the reversed group. There were four perioperative deaths, two in each group, all from myocardial infarction. Primary cumulative patency rates calculated by life-table analysis showed no significant difference at any time after insertion for the two types of graft (Figure 1).

Patency rates were compared for grafts ≥ 4 mm and < 4 mm in diameter. There was a significantly lower cumulative patency rate in grafts of < 4 mm in diameter at all times after surgery (Figure 2) ($P < 0.002$, log rank test). The two techniques were compared for the subgroup of veins of < 4 mm in diameter and no significant difference was found (Figure 3).

Discussion

The *in situ* technique for saphenous vein grafting in the lower limb was described by Hall⁹ in 1964. It has several theoretical advantages. Preservation of endothelial lining leads to a less

thrombogenic flow surface but this may be offset by de-endothelialization caused by valve strippers¹⁰. Preservation of the vasa vasora maintains a living compliant vein wall. Measurement of compliance using a phase-locked echo-tracking system¹¹ has shown slightly better preserved compliance in *in situ* grafts¹² but *in situ* and reversed grafts were three times less compliant than normal arteries¹³. The presence of a positive taper confers improved blood flow characteristics, especially in the presence of a stricture¹⁴. Many surgeons feel that the better size match makes anastomosis easier.

There are, however, drawbacks to the *in situ* technique. Persistent valve cusps may lead to early graft thrombosis, and unligated tributaries may require secondary intervention to ligate or embolize arteriovenous fistulae^{15,16}. Difficulties arise when there is insufficient length at the proximal anastomosis and a short interposition graft may be necessary.

Evidence for the superiority of the *in situ* graft has to date been theoretical and anecdotal^{3,4,6,7} with no prospective, randomized trials.

Overall cumulative patency rates in this study were reasonable when compared with those in other series, with 60 per cent of grafts remaining patent 5 years after operation. Comparison of cumulative patency rates for the two techniques did not show any significant difference at any time after surgery. The groups of patients were similar with respect to age, site of anastomosis (infragenicular and supragenicular), vein graft length, incidence of diabetes, and inflow procedures. Vein usage was similar to that in other series. Vein rejection, because of 'unsuitability', was higher in the reversed group, with nine rejections compared with two in the *in situ* group. No advantage was conferred by either technique.

Comparison between veins of different diameter, however, showed markedly reduced cumulative patency rates at all times after operation for small grafts. This difference can be explained only in terms of vein quality, since there was no other significant difference between the two groups. Smaller veins did not perform well, with a cumulative patency rate of only 36 per cent at 5 years and small *in situ* veins fared as badly as small reversed grafts. It may be technically possible to utilize smaller veins by the *in situ* technique, although these results call into question the advisability of employing such veins for either technique. It is probably the case, especially for above-knee grafts, that prosthetic materials will perform considerably better.

This study has shown that neither technique offered any significant long-term clinical benefit and therefore choice of technique may be made by personal preference. The use of small veins is likely to halve the expected long-term patency rate and serious consideration must therefore be given before using these inferior conduits with either technique.

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Surgical workshop

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Efficacy of endoscopic transthoracic sympathectomy assessed by peroperative palmar temperature measurement

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Endoscopic transthoracic sympathectomy for palmar hyperhidrosis was first described¹ in 1978 and is now regarded as the treatment of choice for this condition^{2–4}. Most patients report dry hands immediately on returning from theatre, and about 80 per cent are very much improved thereafter^{3,4}. This paper reports that measurement of palmar temperature during endoscopic sympathectomy is useful in assessing the immediate efficacy of the procedure.

Surgical technique

With a laparoscope introduced through the fourth intercostal space in the anterior axillary line, the sympathetic chain is easily visualized under the parietal pleura running over the necks of the second, third, fourth and fifth ribs. Where it is not visible the chain may be palpable with the diathermy probe along the neck of each rib. Coagulation of the second, third and fourth thoracic ganglia and intervening chain is achieved using diathermy, and a characteristic charred appearance results. Using a disposable skin temperature sensor (Mallinckrodt, Northampton, UK) affixed to the patient's palm on the relevant side, temperature changes have been measured during six sympathectomies. For the duration of each assessment all other factors, including anaesthetic agents used, have been kept constant.

Table 1 Palmar temperature changes on the operated side during endoscopic transthoracic sympathectomy

Temperature immediately before sympathectomy (°C)	Temperature 3 min after coagulation of sympathetic chain (°C)
33.5	36.1
33.2	34.3
32.5	34.1
33.1	34.4
32.9	34.8
34.3	35.5

Results

A palmar temperature rise of 1.1–2.6 (mean 1.6) °C was recorded on the relevant side within 3 min of coagulation of the sympathetic chain (Table 1) ($P < 0.03$, Wilcoxon matched pairs test). Palmar temperature measurements on the unoperated side remained unchanged during contralateral sympathectomy. The average palmar temperature rise of 1.6 °C seemed to predict a good outcome in that all patients reported sustained abolition of palmar sweating after 6 months; longer follow-up is not yet available.

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Success rates for rehabilitation of vascular amputees: implications for preoperative assessment and amputation level

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All lower limb amputations performed during 1986 and 1988 in eight hospitals in the south-east region were assessed. Of 440 amputations for vascular disease, 193 were above-knee, 193 below-knee, 15 Gritti-Stokes, 15 through-knee and 24 bilateral. Of the 440 patients, 75 died in hospital, 113 were considered unsuitable for a prosthesis and 252 (57 per cent) were referred for prostheses. Rehabilitation questionnaires were sent to 179 patients (41 per cent), as a further 54 had died and 19 had become known non-wearers before the study commenced. The response rate was 81 per cent; 102 patients completed the questionnaire, 21 were reported dead, and 22 were non-wearers. Of a maximum rehabilitation score of 12, 52 patients scored 6 or more (consistent with mobility on their artificial limb around the home), and 21 scored 9 or more (a standard accepted as successful rehabilitation). It is concluded that 10-15 per cent of amputees achieve mobility around the home on their prosthesis. Only 5 per cent, however, rehabilitate well and become independent of their wheelchair. When amputation is inevitable, more consideration should be given to surgery that optimizes wheelchair rehabilitation.

A total of 5000 lower limb amputations for vascular disease are performed annually in the UK¹, and below-knee (BK) amputation results in the best rehabilitation²⁻⁷. When a more proximal amputation is needed, the above-knee (AK) level is often preferred to more distal amputations, such as through-knee (TK) or Gritti-Stokes (GS), because of the high rate of successful primary healing and the cosmetically more attractive prosthesis⁸. However, there have been several recent studies suggesting that rehabilitation after TK amputation may be better than that at the AK level⁹⁻¹¹.

After surgery, one of the main concerns is successful mobilization. However, many patients will never walk on an artificial limb, and realistic appraisal in these cases will judge a good wheelchair to be more appropriate than a prosthesis. This knowledge might affect amputation level. In the wheelchair-bound patient the GS amputation, with its long lever and good record of primary healing, is superior to the AK operation¹²⁻¹⁴.

Information on amputees under the care of the disablement services centres (DSCs) suggests that 50 per cent of them rehabilitate successfully and only 5 per cent are totally dependent on their wheelchairs^{11,15}. Studies based on the DSCs are, however, inevitably biased towards current limb wearers, many of whom are young traumatic amputees who rehabilitate well. Very little is known about the outcome for more elderly amputees with vascular disease. How many are referred for prosthetic fitting and how many rehabilitate successfully? Are too many patients referred for prostheses? Should more GS or TK amputations be performed in patients who are likely to be wheelchair bound? Knowledge of the outcome of operations should help surgeons to tailor amputations to the needs of individual patients. This study was designed to answer the above questions.

Patients and methods

Operating theatre records were examined to determine the date and level of all amputations for vascular disease performed at eight hospitals in the south-east region for the periods January to December 1986, and January to December 1988. The number of amputations requiring

revision was determined as was the number of patients dying while in hospital. The number of patients referred from each hospital for prosthetic fitting was then assessed by access to the DSC notes. The reasons for patients not being referred for prosthetic fitting related to a mix of medical, social and psychological factors and were not studied in detail.

By scrutiny of the DSC notes and from questionnaires it was determined how many patients had died or become non-wearers since referral for prosthetic fitting. Questionnaires were then sent to all the recorded current limb wearers. Rehabilitation was assessed by the answers to four standard questions:

1. Do you use your limb to walk:
(a) less than 25 per cent of waking hours (score 0)
(b) between 25 and 50 per cent of waking hours (score 1)
(c) more than 50 per cent of waking hours (score 2)
(d) all waking hours (score 3)
2. Do you use your limb to walk:
(a) just when visiting your doctor or limb-fitting centre (score 0)
(b) at home but not to go outside (score 1)
(c) outside the home on occasions (score 2)
(d) inside and outside all the time (score 3)
3. When going outside wearing your limb do you:
(a) use a wheelchair (score 0)
(b) use two crutches, two sticks or a walking frame (score 1)
(c) use one stick (score 2)
(d) use nothing (score 3)
4. When walking with your limb outside do you feel unstable when:
(a) walking on the flat (No: score 1)
(b) walking on slopes (No: score 1)
(c) walking on rough ground (No: score 1)
(Yes to any of (a)-(c): score 0)
(Amputees who used a wheelchair outside scored 0 for this question.)

The patients were also asked whether they had a wheelchair and for how many of their waking hours they used it. The answers to these questions were analysed to assess the patient's wheelchair dependence. Statistical differences between the types of amputation were assessed using the Mann-Whitney *U* test.

Results

In the 2 years studied, 440 vascular lower limb amputations were performed in the eight hospitals: 232 in 1986 and 208 in

Table 1 Age distribution and number of the different amputation types

Amputation	n	Median age (years)
Above-knee	193	72 (39–90)
Below-knee	193	70 (39–93)
Gritti–Stokes	15	79 (65–94)
Through-knee	15	81 (44–90)
Bilateral	24	72 (50–85)

Values in parentheses are ranges

Table 2 Age and rehabilitation of limb users responding to the questionnaire

Amputation	n	Median age (years)	Median rehabilitation score
Above-knee	31	68 (50–85)	4 (1–9)
Below-knee	56	68 (49–88)	6 (0–11)
Gritti–Stokes	3	81 (78–86)	9 (3–9)
Through-knee	1	81	7
Bilateral	11	67 (50–85)	1 (1–10)

Values in parentheses are ranges

1988. Of 212 BK amputations (48 per cent), 19 failed to heal, resulting in a revised higher amputation. Of the 440 healed amputations, 193 were AK, 193 BK, 15 GS, 15 TK and 24 bilateral. The age distribution is shown in Table 1. A total of 25 amputations had required revision (19 of which were BK to AK). Of the 440 patients, 75 (17 per cent) died without leaving hospital and 113 (26 per cent) were considered unsuitable for artificial limbs.

There were 252 amputees (57 per cent) referred for prosthetic fitting. Before the start of the study, 54 patients in this group were known to have died and 19 had become non-wearers. The rehabilitation questionnaire was therefore sent to 179 patients. Information was received from 81 per cent of these with 21 patients being reported dead, 22 to be non-wearers, and 102 filling in the questionnaire. Thus, of the original 252 referred for prosthetic fitting, 75 (30 per cent) had died (49 from 1986 and 26 from 1988) and 41 had become non-wearers (25 from 1986 and 16 from 1988). Of the original 440 patients, 102 (23 per cent) completed the rehabilitation questionnaire, reporting on 31 AK, 56 BK, 11 bilateral, three GS and one TK amputations. The rehabilitation scores and age distribution of these patients are shown in Table 2. It should be noted that no reply was received from 19 per cent of patients, despite attempts to telephone and visit them at home.

Rehabilitation

A score of 9 was accepted as satisfactory rehabilitation and one of 6 as indicating mobility on the prosthesis around the home; 52 patients scored 6 or more and 21 9 or more. Therefore, 12 per cent of the initial 440 amputees became mobile on their limb around the home, but only 5 per cent achieved satisfactory rehabilitation. Of the 177 amputees referred for limb fitting who were still alive, 29 per cent were mobile on their limb around the home and 12 per cent were satisfactorily rehabilitated.

BK amputees performed better than AK ones. Of all the current limb wearers 55 per cent were BK and 30 per cent AK amputees (the original numbers of AK and BK amputees were the same). The remaining 15 per cent comprised bilateral (11 per cent), GS (3 per cent) and TK (1 per cent). The numbers of these amputation types were too small to assess comparative rehabilitation. Of the original 193 BK amputees, 31 (16 per cent) had a rehabilitation score of 6 or more and 5 per cent of 9 or more. This compares with respective figures of 9 and 4 per cent for AK amputees. The BK amputees also had a higher median rehabilitation score, although this was

not statistically significant. Of the original 24 bilateral amputees, four (17 per cent) rehabilitated satisfactorily to a score of 9 or more.

Wheelchair use

Of limb users, 91 per cent from 1986 and 96 per cent from 1988 possessed a wheelchair. Of these, 26 per cent never used it, 19 per cent used it for between one-quarter and half of their waking hours, 41 per cent used it for more than half of their waking hours, and 15 per cent used it all the time.

Discussion

The numbers of patients who were satisfactorily rehabilitated in this study (5 per cent) and who became mobile around the home (12 per cent) are in agreement with the results of a previous Swedish study, in which 13 per cent of 126 amputees used their prosthesis 2 years after amputation¹⁶. These findings do, however, contrast with figures of around 50 per cent in other studies^{11,15}, which involved only limb wearers under the care of DSCs. In the current series all patients undergoing surgery were followed, and the much lower rates of successful rehabilitation take into account those who died or were not referred to DSCs. This emphasizes that amputees comprise two distinct groups: relatively fit and often young traumatic patients who survive for a long time and rehabilitate well¹⁷, and older medically unfit amputees with vascular disease and a poor prognosis. In the present series, the median age of the amputees was 70 years or more. Although amputation for trauma comprises only 7 per cent of all operations¹⁸, because of the long survival in this group it represents over 50 per cent of amputees under the care of DSCs¹¹.

Only half of the amputees in the present series were referred for prosthetic fitting, and two-thirds of these either died within 3 years or did not wear their artificial limb. Almost twice as many BK amputees became mobile around the home on their prosthesis as AK amputees. This supports the conclusion from other series that the knee joint should be preserved wherever possible^{2–7}. Very few TK or GS amputations were performed in this study and no conclusions can be drawn regarding these.

We believe that realistic advice on prostheses before surgery is very important for the vascular patient, who should be assessed before operation by an amputation team that includes a physiotherapist and an occupational therapist. The presence of arthritis, gait abnormality or neurological deficit might contribute to non-referral for limb fitting. It should be possible to develop criteria that will help to predict whether a patient will achieve successful mobilization on a prosthesis. These could then be used as guidelines for the surgeon and patient in deciding the level of amputation. After operation, every effort should be made to avoid delays in mobilization and rehabilitation⁷.

If the intention is to fit a prosthesis, BK amputation is preferred to all other levels. If this is impossible, consideration should be given to the TK procedure. In many patients poor blood supply contraindicates both the BK and TK levels, but a few may still be suitable for TK amputation. The TK operation has fallen into disrepute because of its lower primary healing rate compared with the AK level. It does, however, have certain advantages, including a lower in-hospital and subsequent mortality rate¹⁹, increased stability when transferring and sitting, reduced dependence on long-term nursing care¹⁹, and better rehabilitation on a total end-bearing stump^{9–11}. If prosthetic fitting is not considered appropriate, the longer stump of the GS or TK amputation may be preferable to the standard AK amputation. Of these two, the GS is preferable as the primary healing rate is superior^{12–14}.

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Short note

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Continuous ambulatory peritoneal dialysis in patients with aortic grafts

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In the UK there are over 7600 patients maintained on dialysis for treatment of renal failure¹; 56 per cent are managed by haemodialysis and 44 per cent by continuous ambulatory peritoneal dialysis (CAPD). Since its introduction² in 1976, CAPD has found increasing application in these patients^{3,4}.

Many aetiological factors are common to both renal failure and peripheral vascular disease, and as dialysis is made available to an older population the incidence of dual pathology will increase. Aortic reconstruction using synthetic vascular grafts is an established surgical procedure and the avoidance of septic complications is of paramount importance because subsequent management is accompanied by high mortality and morbidity rates⁵.

Patients undergoing long-term haemodialysis require surgical formation of an arteriovenous fistula for dialysis access⁶. In arteriopathic patients with poor vasculature the creation of a fistula may be impossible and such patients are more suitable for CAPD. However, there has been understandable reluctance to introduce CAPD catheters into the peritoneal cavity of a patient with an aortic graft because of the high

incidence of peritonitis associated with this form of dialysis⁷ and the subsequent risk of graft infection. Five patients with synthetic aortic grafts in whom end-stage renal failure was successfully managed using CAPD are reported.

Patients and methods

There are currently 264 patients with end-stage renal failure being treated at Leicester General Hospital: 158 by CAPD and 106 by haemodialysis. There has been a policy in the past 3 years to use CAPD wherever possible in patients with aortic grafts.

Six patients with a history of synthetic aortic reconstruction were identified in whom end-stage renal failure was managed using either CAPD (five patients) or haemodialysis (one).

All the patients undergoing CAPD were men, with an age range of 36-69 (mean 59.2) years. Two had been maintained on dialysis before aortic surgery: one had undergone haemodialysis for 15 years, the other CAPD for 15 months. This patient was transferred for perioperative haemodialysis. In two patients renal failure was precipitated by aortic surgery. Although both of these had pre-existing renal disease, their aneurysms arose below the renal arteries. In the fifth patient renal failure occurred 7 years after aortic reconstruction. Patient details are summarized in Table 1.

Vascular reconstruction was undertaken using a woven Dacron (Du Pont, Stevenage, UK) prosthesis in all cases. Three patients received bifurcation grafts and two had straight grafts. In all patients undergoing aneurysm repair the wall of the aneurysm was closed around the graft. The aorta was reperitonealized in all but one case, in which this procedure was found to be technically impossible.

All CAPD catheters were inserted using a standard procedure. Under general anaesthesia a short infraumbilical incision was made and the peritoneum approached via a longitudinal paramedian rectus abdominis split. The peritoneum was opened and a silicone peritoneal dialysis catheter with an extraperitoneal Dacron cuff (Quinton, Uxbridge, UK) placed in the rectovesical pouch. The catheter was tunnelled subcutaneously away from the incision. All patients received antibiotic prophylaxis with 1.5 g cefuroxime intravenously on induction of anaesthesia.

Minor difficulties arose from intra-abdominal adhesions both to the previous scar and within the pelvis; however, these did not prevent successful catheter placement.

Short note

Table 1 Patient details

Patient no.	Age (years)	Sex	Diagnosis		Interval between aortic and CAPD surgery
			Renal	Vascular	
1	69	M	End-stage renal failure secondary to hypertension and renovascular disease	Abdominal aortic aneurysm	30 days
2	64	M	End-stage renal failure secondary to hypertension and renovascular disease	Abdominal aortic aneurysm	17 weeks
3	36	M	Alport's syndrome	Abdominal aortic aneurysm	5 years
4	60	M	Polycystic kidneys	Abdominal aortic aneurysm	3 months
5	67	M	Polycystic kidneys	Occlusive aortoiliac disease	7 years

CAPD, continuous ambulatory peritoneal dialysis

Table 2 Complications

Patient no.	Complications of CAPD	Complications of vascular graft	Follow-up	Outcome
1	None	None	> 2 years	CAPD and graft functioning
2	Peritonitis (culture negative) Peritonitis (<i>Escherichia coli</i>) Exit site infection	None	> 2 years	CAPD and graft functioning
3	Exit site infection	None	7 months	CAPD and graft functioning
4	Peritonitis (<i>Klebsiella oxytoca</i>)	None	6 months	CAPD and graft functioning
5	None	None	> 2 years	CAPD and graft functioning

CAPD, continuous ambulatory peritoneal dialysis

Results

After operation there were three episodes of peritonitis in two patients. These were successfully treated with a 10-day course of intraperitoneal vancomycin and gentamicin. A summary of the complications following CAPD catheter insertion is shown in Table 2.

At the time of review the mean follow-up was 18.2 (range 6–26) months. All patients were successfully maintained by CAPD. There have been no episodes of aortic graft infection or dysfunction.

The one patient maintained by haemodialysis was not transferred to CAPD for social reasons. He underwent an aortobifemoral graft for an infrarenal aneurysm; haemodialysis had been established shortly before this for long-standing renal failure. There were no problems with the graft or dialysis.

Discussion

In arteriopathic patients with aortic grafts and renal failure there is no ideal treatment option. Haemodialysis requires either creation of a permanent arteriovenous fistula with repeated cannulation, or placement of a temporary percutaneous venous catheter. Both may be responsible for episodes of bacteraemia. The shortage of organ donors, together with the problem of finding a suitable site for transplant anastomosis, excludes most of these patients from renal transplantation.

The causes of vascular graft infection have been identified⁶ as direct operative contamination or later bacteraemia. Transient bacteraemia may result from such procedures as endotracheal intubation, bladder catheterization or intravenous cannulation. It may also arise from a distant focus of infection⁷. In this context it may be important to reperitonealize the aorta wherever possible to re-establish a definite barrier between peritoneum and graft.

The presence of a CAPD catheter provides an obvious route for infection. Despite the instruction of patients in strict aseptic technique, peritonitis is a common complication⁷. However, the macroscopic examination of dialysis fluid facilitates the

early diagnosis of infection, often before the development of other symptoms, allowing prompt initiation of treatment.

This paper confirms that the presence of a synthetic aortic graft is not an absolute contraindication to the use of CAPD for the treatment of renal failure⁸. Close surveillance of these patients is clearly mandatory and the possibility of infection must be entertained at all times.

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Systemic cytokine response after major surgery

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The systemic cytokine response to major surgical trauma was studied in 20 patients undergoing elective aortic surgery and five patients after inguinal hernia repair. Tumour necrosis factor alpha and interferon gamma were not detected in these patients. An early and short-lived interleukin 1 beta (IL-1 β) response to major surgery was detected only by intensive sampling in the perioperative period. The IL-1 β peak preceded a more marked interleukin 6 (IL-6) response that peaked 4-48 h after surgery. IL-6 levels had fallen sharply by 48-72 h in all patients who had an uneventful postoperative course. The IL-6 peaks were significantly lower after hernia surgery than after major aortic operations ($P < 0.001$); IL-1 β was not detected in any samples. Three patients undergoing aortic surgery developed unexpected major postoperative complications. IL-6 levels in this group were significantly higher than those of the other patients undergoing aortic surgery within 6-8 h of skin incision, and remained elevated for longer. These rises in plasma IL-6 levels preceded the clinical onset of major complications by 12-48 h. The systemic IL-1 β and IL-6 response to surgical trauma increased with the severity of the surgical insult. An early, exaggerated IL-6 response was associated with the subsequent clinical development of major complications.

Surgery and trauma induce a generalized state of immunodepression¹ that correlates with sepsis² and late death³. Cytokines, which are polypeptides produced by cells of the immune system and a variety of other tissues, act as mediators of the immune and acute-phase responses. Each cytokine mediates a variety of frequently overlapping effects and their actions can be additive.

Tumour necrosis factor alpha (TNF- α), interleukin 1 beta (IL-1 β) and interleukin 6 (IL-6) are major mediators of the acute-phase response in humans. TNF- α and IL-1 β are considered to be primarily responsible for the non-hepatic manifestations of the response such as fever, elevated prostaglandin levels, tachycardia and accelerated catabolism⁴. IL-6 *in vitro* is primarily responsible for the hepatic component of the acute-phase response, resulting in the synthesis of acute-phase proteins^{5,6}. IL-1 β and TNF- α also induce synthesis of acute-phase proteins, in particular C-reactive protein (CRP)⁷⁻⁹. The transcription and production of IL-6 in fibroblasts, endothelial cells, keratinocytes and monocytes is enhanced *in vitro*¹⁰⁻¹³ by IL-1 β and TNF- α . There is evidence, therefore, that IL-1 β and TNF- α may be partly responsible for the induction of IL-6. All of these cytokines may then mediate the acute-phase response.

These cytokines all have immunostimulatory capabilities; interferon gamma (IFN- γ) acts primarily on monocytes and macrophages to enhance cell-mediated cytotoxicity. The release of these cytokines may therefore represent an attempt by the body to counter the observed immunodeficiency associated with injury or sepsis. Immunotherapy in oncological and inflammatory conditions centres around the evaluation of the administration of cytokines and their inhibitors in various disease states.

The measurement of cytokines in the peripheral blood has proved difficult and most reports in humans have been of sporadic detections involving single or daily measurements. There have been few attempts to assay cytokines over a series of times during an acute illness or after severe trauma. TNF- α has seldom been detected except after endotoxin administration, which does not induce a detectable IL-1 β response *in vivo*¹⁴. Shenkin *et al.*¹⁵ recently detected a consistent rise in the serum

concentration of IL-6 in elective surgical patients but were unable to detect such a rise in IL-1 β or TNF- α ; these patients had an uncomplicated clinical course and the difference between a pathological and a physiological IL-6 response remains unclear.

This study examined patients before, during and after major surgery, exploring the association between plasma cytokine levels, the clinical course and CRP response. The levels of IL-1 β , IL-6, TNF- α and IFN- γ were assessed in patients undergoing elective aortic aneurysm surgery. This provided a relatively uniform population in terms of age and general health undergoing comparable surgical insult. The patients did not have malignant disease and were at relatively low risk of bacterial contamination and sepsis. The impact of major surgical trauma on cytokine levels was therefore evaluated without the conflicting influences of bacterial infection or malignancy on the immune system.

A smaller group of patients undergoing inguinal hernia repair was assessed to determine whether the cytokine response was related to the magnitude of surgical trauma.

Patients and methods

Subjects

Group 1 consisted of 20 patients (17 men and three women) aged between 59 and 83 years undergoing elective aortic aneurysm repair. Operative and postoperative details were recorded, including the duration of operation, aortic clamping and ventilation, the blood transfusion volume, postoperative temperature, leucocyte count and APACHE II scores. APACHE II scoring was performed on the initial and worst physiological parameters during the first 24 h after surgery.

Group 2 consisted of five patients (four men and one woman) aged between 55 and 78 years who underwent elective inguinal hernia repair. The studies were approved by the Central Oxford Research Ethical Committee.

Samples

Cold-spun plasma was prepared from venous blood collected in pyrogen-free tubes containing ethylenediamine tetra-acetic acid (0.34 mmol/l). Aliquots of plasma were stored at -70°C . A preliminary study showed that using tubes containing aprotinin conferred no advantage.

Sample times

Samples were taken the day before and immediately before surgery after induction of anaesthesia. They were drawn at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6, 8, 12, 24 and 48 h after surgery and daily thereafter. Samples were drawn from patients in group 2 until their discharge 24 h after surgery.

Cytokine assays

IL-6, IL-1 β and IFN- γ levels were measured using commercially available 'sandwich' enzyme-linked immunosorbent assay (ELISA) methods (IL-6 from R & D Systems, British Biotechnology, Oxford, UK; IL-1 β and IFN- γ from Medgenix Diagnostics, High Wycombe, UK). TNF- α concentration was measured by ELISA using a murine monoclonal antibody as previously described¹⁶. In each assay a standard curve using recombinant cytokine was constructed and each sample assayed in duplicate. The minimum sensitivity of the assay was 3 pg/ml for IL-1 β and IFN- γ , 4 pg/ml for IL-6 and 10 pg/ml for TNF- α . Twenty random samples were assayed independently for IFN- γ using a different ELISA at the National Institute for Biological Standards and Controls, Hertfordshire, UK (minimum sensitivity 10 μ g/ml).

C-reactive protein assay

CRP was measured using flow nephelometry (Array Protein System; Beckman Instruments, High Wycombe, UK) with a minimum detectable level of 6 mg/l.

Statistical analysis

Data were analysed using the Mann-Whitney *U* test and Spearman rank correlation coefficient (r_s).

Results

Clinical

Eight patients in group 1 had an uncomplicated postoperative course. Nine patients in this group suffered minor complications. Five of these had respiratory complications including atelectasis and bronchopneumonia, of whom three were treated with a short course of antibiotics in addition to physiotherapy and oxygen. Another patient developed distal ischaemia in one foot and mild congestive cardiac failure, one developed atrial fibrillation which was successfully managed with digoxin, and one had bilateral groin infections and a urinary tract infection. Transient acute tubular necrosis developed in the ninth patient, whose plasma creatinine rose from 108 mmol/l before surgery to 209 mmol/l on day 3. She responded promptly to dopamine and colloid infusion. None of these complications delayed discharge from hospital; the longest postoperative stay was 12 days.

Three patients in group 1 suffered profound complications. One patient with chronic obstructive airway disease was thought to be progressing well but developed hypotensive shock 36 h after surgery. Abdominal distension with no evidence of sepsis prompted laparotomy at 50 h which was normal. Pus was then aspirated from the bronchial tree and antibiotic therapy started for septicaemia secondary to pneumonia. The patient made a slow recovery and was discharged 3 months after admission. A second patient was discharged from the intensive care unit after 22 h with a satisfactory urine output and was thought to be doing well. At 36 h renal function was noted for the first time to be grossly abnormal and intractable renal failure and pneumonia ensued. An emergency cholecystectomy for gallbladder infarction was required 1 week later and 3 weeks later a left hemicolectomy for ischaemic colitis was performed. The patient was discharged to a high-dependency nursing home after 7 months in hospital. The third patient appeared well after surgery and did not require admission to the intensive care unit. Renal failure was diagnosed at 24 h, when the patient became oliguric with a serum creatinine level of 308 mmol/l, and dialysis was begun. A bleeding peptic ulcer required oversewing and the following day sigmoid colectomy was needed for bowel infarction. This patient died on day 13 after operation from adult respiratory distress syndrome.

All patients undergoing herniorrhaphy were discharged on the first day after operation without complications.

Interleukin 6

Low levels of this cytokine were detected before operation in five of the 25 patients studied. In group 1 there was an early, continuous rise after about 90 min, peaking at 4–48 (median 8) h and falling rapidly thereafter in all patients with an uncomplicated postoperative course. The three patients with major complications each had a greater and more prolonged response (Figure 1) which was apparent during surgery or within 8 h of incision, and was well in advance of clinical suspicion of complications. No cytokines were detectable in stored blood before transfusion.

The IL-6 response in group 2 showed similar kinetics to that in group 1 and concentrations peaked at 4–12 (median 8) h after incision, but were significantly lower (6, 20, 21, 51 and 37 pg/ml) ($P < 0.001$), with the highest IL-6 level seen in the only patient who underwent bilateral inguinal hernia repair.

Recent criticism of the use of peaked curves in the analysis of serial biological measurements prompted a comparison of this method with that of summary measures, which requires the calculation of the area under the response curve¹⁷. Peak IL-6 levels were found to correlate well with the response derived from the area under the IL-6 curve ($r_s = 0.88$, $P < 0.001$) (Figure 2).

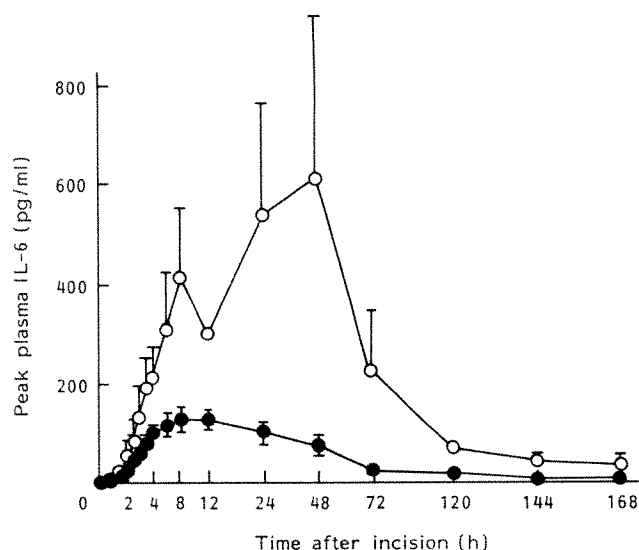


Figure 1 Mean (s.e.m.) peak plasma interleukin 6 (IL-6) responses in 20 patients undergoing elective aortic surgery with (○, $n = 3$) and without (●, $n = 17$) major postoperative complications. $P < 0.05$ (3.5–6 h); $P < 0.01$ (8–48 h); $P < 0.001$ (72–120 h); Mann-Whitney *U* test

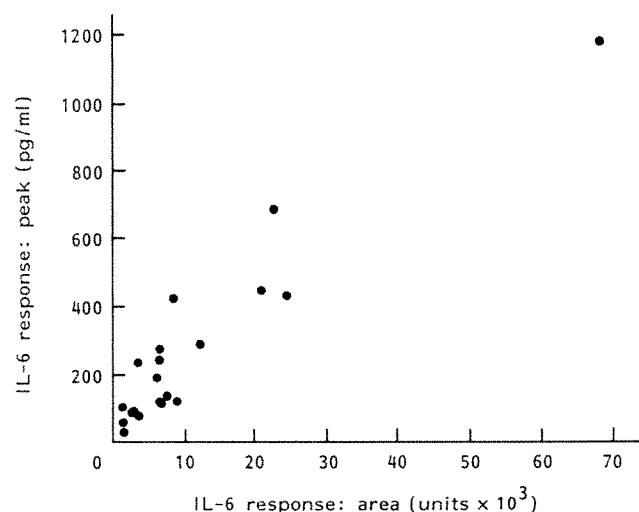


Figure 2 Correlation between interleukin 6 (IL-6) response measured by peak concentration and area under the curve methods. $r_s = 0.88$, $P < 0.001$

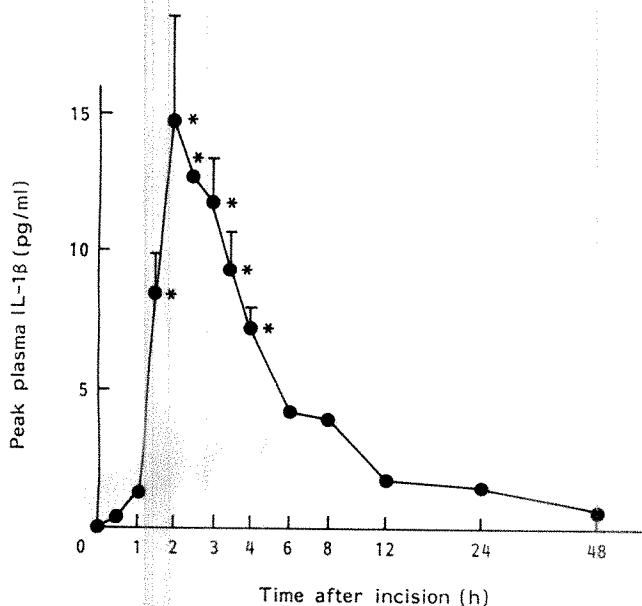


Figure 3 Mean (s.e.m.) peak plasma interleukin 1 beta (IL-1 β) responses in 20 patients undergoing elective aortic surgery. * $P < 0.001$ (times indicated versus 0.5 h, Mann-Whitney U test)

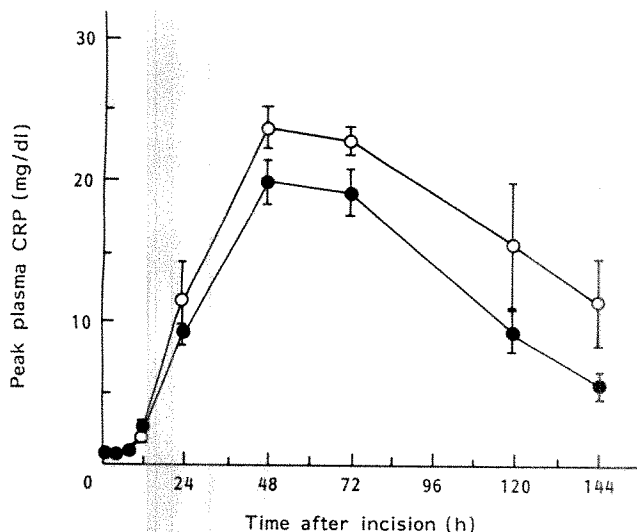


Figure 4 Mean (s.e.m.) peak plasma C-reactive protein (CRP) responses in 20 patients undergoing elective aortic surgery with (○, $n = 3$) and without (●, $n = 17$) major postoperative complications

Interleukin 1 beta

Between 1 and 4 h after surgery, a brief rise in IL-1 β was detected in 17 patients in group 1 (Figure 3). In each patient the rise preceded the IL-6 response by several hours and disappeared rapidly. There was no significant difference in the IL-1 β response of patients with complicated and uncomplicated courses. IL-1 β was not detected in any group 2 patient.

Interferon gamma

IFN- γ was not detected by either ELISA in any sample.

Tumour necrosis factor alpha

TNF- α was detected in only one sample (42 pg/ml), which was taken at 12 h from the third patient with complications.

C-reactive protein

An increase in plasma CRP was apparent at 12 h (Figure 4) and, although levels were slightly higher in the patients with complications, the difference was not statistically significant

and was not apparent until 48 h, by which time complications were clinically evident.

Correlations were sought between the clinical data presented and the cytokine response. A weak correlation was seen between the IL-6 response and the APACHE scores ($r_s = 0.44$, $P = 0.05$), between IL-6 and the blood transfusion volume ($r_s = 0.49$, $P = 0.03$), and between the peak CRP and IL-1 β responses ($r_s = 0.60$, $P = 0.02$). There was no correlation between the IL-1 β and IL-6 responses, nor between levels of either of these cytokines and postoperative temperatures or leucocyte counts, or the duration of operation, aortic clamping or ventilation.

Discussion

The early and brief IL-1 β response to major surgical injury always preceded the IL-6 response in any individual patient. These data provide evidence consistent with the observation *in vitro* that IL-1 β induces IL-6 synthesis and release¹⁰⁻¹³. The absence of any correlation between the IL-1 β and IL-6 responses may be less consistent with this conclusion but might be explained by the action of IL-1 β being more local with a less consistent overflow into the peripheral circulation than seen with IL-6. An IL-1 β receptor antagonist has recently been described¹⁸ and differences in the concentration of this might cause similar IL-1 β concentrations to induce different IL-6 responses in different patients.

IL-1 β has only occasionally been detected in the peripheral plasma, for example in four patients with meningococcal septicaemia¹⁹. In most studies where IL-1 β was not detected the patients were sampled only daily, and the period when detectable IL-1 β might have been present could easily have been missed. When human volunteers were administered TNF- α and endotoxin, IL-1 β was not detected in the circulation^{14,20} but no samples were taken between 1 and 3 h; alternatively, the radioimmunoassay used in the latter study might have been less sensitive than the ELISA used in the present work, which has shown that an IL-1 β response will be detected only by frequent sampling during operation or in the equivalent period after major injury.

The IL-6 response observed in the 17 patients undergoing surgery with either minor or no complications is similar to that published in two recent reports^{21,22}. The IL-6 levels of the three patients with major complications rose above the mean within a few hours of incision, well in advance of their subsequent complications. In each case there was no suspicion of poor progress until 24–48 h had passed. Their IL-6 response not only preceded their clinical signs by 12–36 h but was significantly greater and persisted longer than the response seen in the group with lesser complications.

IL-6 is released by most body tissues and its plasma concentration may therefore provide a measure of tissue damage during injury. The smaller IL-6 response seen in patients in group 2 is consistent with this hypothesis. The surgeon is unable to assess tissue damage at the cellular level resulting from harmful influences such as ischaemia and changes in pH. Such tissue damage may induce the observed early rise of IL-6, either directly or via IL-1 β mediation. These intraoperative changes may have a direct impact on the subsequent development of major complications and may be reflected in the correlation between IL-6 concentration and APACHE II score.

There have been many attempts to correlate isolated cytokine levels with prognosis, the most notable of these involving TNF- α . Although the increases have not been consistent, circulating levels of TNF- α have been associated with poor clinical outcome in patients with sepsis or burns^{16,19,23,24}. Serum levels of TNF- α have been shown to have a negligible impact on the prediction of outcome when assessed in conjunction with simple clinical and laboratory variables²⁵. Despite intensive sampling and the use of a sensitive

immunoassay, TNF- α was not detected in the patients in this or a similar study²². TNF- α has been detected in plasma 90–120 min after endotoxin administration¹⁴, which corresponds to the period of IL-1 β appearance in this study. A very low concentration of TNF- α is possibly present which, along with IL-1 β , might be involved with IL-6 induction at this time. Alternatively, endotoxin might induce different cytokine responses from surgical trauma.

Plasma IL-6 concentration has been shown to correlate with duration of surgery for a wide range of elective operations^{15,21}. In this study of a single major surgical procedure no correlation with the length of surgery was observed. The duration of many operations influences the extent of surgical tissue injury and perhaps IL-6 release; this may not be as true of aeurysm surgery in which ischaemia and marked changes in blood pressure may be more important determinants of cell damage than the duration of surgery. Blood transfusion requirement may be a better reflection of surgical trauma than operative duration and this may explain the weak but significant correlation between IL-6 levels and blood transfusion requirements.

The CRP response confirms that described in previous studies^{26,27}, and the 20–30-h delay between the appearance of the cytokines and the CRP response is consistent with *in vitro* and *in vivo* evidence that IL-1 β and IL-6 are mediators of acute-phase protein synthesis^{28,29}. The results of this study suggest that CRP is less sensitive than IL-6 as a marker of surgical complications. The comparatively slow CRP response times of about 48 h mean that this polypeptide has little predictive clinical value and its utility in the early postoperative period has proven limited.

This study demonstrates that IL-1 β and IL-6 responses increase with the severity of the surgical insult and that IL-6 levels are maximal in patients who go on to develop major complications. Routine measurement of IL-6 after major surgery may have a valuable role in identifying patients in need of careful postoperative monitoring. Further studies are needed to determine whether the plasma IL-6 concentration simply reflects the degree of tissue insult or whether it plays a more active role in induction of, or defence against, postoperative complications.

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Continuing experience with transaxillary excision of the first rib for thoracic outlet syndrome

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The results of transaxillary excision of the first rib for thoracic outlet syndrome are reported. During a 3-year period, 40 transaxillary rib resections were performed on 32 patients. The symptoms in 33 limbs were completely relieved and in a further four symptoms were improved. These results confirm that transaxillary excision of the first rib is the operation of choice in the management of thoracic outlet syndrome.

Thoracic outlet syndrome continues to present the vascular surgeon with problems of both diagnosis and management. The experience of one unit using transaxillary resection of the first rib in the treatment of this condition is reported.

Patients and methods

Consecutive patients with a clinical diagnosis of thoracic outlet syndrome submitted to operation under the care of the senior author (J.H.H.W.) in the 3-year period September 1988 to September 1991 were reviewed. For the first 28 of these patients, demographic data, symptoms, investigative procedures, operative details and outcome were gathered from case notes, supplemented by telephone interview. Since January 1991, these data have been recorded prospectively and entered into a computer database. All patients were treated by transaxillary excision of the first rib (and cervical rib if present); the operative details have been reported previously¹. The outcome was assessed simply as complete, partial or no relief, as previous authors have found that more complex grading adds little².

Results

During the study period a total of 40 first rib excisions were performed on 32 patients (28 female, four male). The median age was 37 (range 12-58) years. Only three of the patients were primary referrals from their general practitioners; 18 were secondary referrals from other surgeons and 11 came from physicians.

Cervical ribs were apparent on chest radiography or at operation in eight patients and were bilateral in five of these. An additional two patients had an abnormal first rib. A history of trauma, either a fall on to the arm or, more commonly, a whiplash injury to the neck, was obtained from seven patients.

The median duration of symptoms was 2 years (range 2 weeks to 28 years). Nine patients had symptoms of arterial compression, including one who presented as an emergency with an ischaemic arm. Ten were thought to have a combined neurological and vascular symptomatology, and 11 had a purely neurological pattern. Only two patients had venous symptoms, one acute, the other chronic. The bilateral symptoms in eight patients were similar on both sides.

On examination, the Roos test was positive in 29 patients. Two-position subclavian arteriography was performed in 18 patients, demonstrating abnormality in 11. In the nine with arterial symptoms, an arteriogram gave abnormal findings in all but one. The patient presenting with arm ischaemia had blockage of the brachial artery by subclavian emboli, two patients had narrowing of the artery as it passed over the rib with poststenotic dilatation, and the others demonstrated narrowing of the artery when the arm was abducted. Six of those with neurovascular symptoms underwent arteriography, which showed narrowing of the artery in abduction in half, but was normal in the remainder. Three patients with neurological symptoms had normal arteriograms. Duplex ultrasonography was used in eight patients and demonstrated abnormalities later confirmed angiographically in seven. Venography was

Table 1 Clinical outcome of transaxillary excision of the first rib (and cervical rib if present)

Symptom type	Relief in response to treatment		
	Complete	Partial	None
Arterial only (n = 13)	10	2	1
Combined neurological and vascular (n = 13)	11	1	1
Neurological only (n = 12)	10	1	1
Venous only (n = 2)	2	—	—
Total (n = 40)	33	4	3

performed in four patients, but was abnormal only in the two with symptoms of venous obstruction. Nerve conduction studies were carried out on ten patients, but were abnormal in only two patients with obvious wasting of the hand muscles, confirming denervation in the C8 and T1 territories. Computed tomography was unhelpful on the four occasions when it was used.

All patients underwent transaxillary excision of the first rib and cervical rib if present. The patient presenting with an acutely ischaemic limb also underwent a subclavian to ulnar artery vein graft; the proximal end of this procedure was performed through a separate supraclavicular incision. The pleura was torn during the course of 18 operations and a temporary chest drain inserted. There were no major complications, but minor morbidity included three chest infections, one wound infection and one pneumothorax. Three patients were troubled by neuralgia from the intercostobrachial nerve, but this was self-limiting in each case.

The median follow-up has been 1 year (range 2-38 months). The outcome is shown in Table 1. The symptoms were improved in 37 of the 40 limbs. Symptoms have so far recurred in only one patient in this series, 20 months after operation.

Discussion

Although it has been appreciated for over a century that neurovascular symptoms in the arm can arise from proximal compression³, this condition continues to provoke much debate. Some authorities deny that thoracic outlet syndrome occurs in the absence of a demonstrable skeletal abnormality⁴, and among those who accept the existence of the syndrome there is discussion as to how it is best treated.

In a proportion of cases there are demonstrable skeletal abnormalities about the thoracic outlet and impinging upon it. The most common of these is a cervical rib, which is found in about one-quarter of patients in series from the UK^{5,6}, but in fewer than 10 per cent of those reported from the USA⁷⁻⁹. Less frequent are abnormalities of the first rib¹⁰ and callus from previous fractures to the ribs or clavicle. The majority of patients have abnormal soft tissue structures, and Roos has

described an array of fibrous bands associated with the scalene muscles¹¹.

It is not well understood why the congenital abnormalities that make these patients prone to symptoms should suddenly exert their effects. Some authorities have speculated that increase or reduction in muscle bulk, or the assumption of a poor posture, may be the precipitant^{11,12}. Sanders *et al.* found that 70–90 per cent of their patients under direct questioning gave a history of trauma, especially whiplash injury to the neck, preceding the onset of symptoms⁷. This has not been supported by the findings of other workers⁸ or of this study, in which only 20–30 per cent had a confirmed history of trauma. This figure is more in accord with the 18 per cent incidence of presumably post-traumatic scalene muscle fibrosis reported by Sanders' group⁷.

The symptoms of thoracic outlet syndrome fit, with some overlap, into three groups. Neurological symptoms consist of pain and paraesthesia, usually in the distribution of the C8 and T1 dermatomes. Arterial involvement is manifested as pain in the entire arm that is precipitated by exercise, especially with the arm abducted; these patients may demonstrate Raynaud's phenomenon. Least common are venous symptoms, which can be chronic or acute, the arm becoming swollen and blue. Roos and other specialists in the USA categorize 90–99 per cent of their patients as having neurological symptoms^{7,11,13}. The findings of the present and other similar studies are that nearer 60 per cent of cases are neurological^{1,5,6}. This disparity has been explained simply by referral patterns of patients to vascular centres¹², but it might indicate an undertreated group of patients with arm complaints.

The major dilemma in the management of thoracic outlet syndrome is the lack of a definitive diagnostic test^{7,9}. Manoeuvres that cause reduction or disappearance of the radial pulse are non-specific, being positive in many normal individuals¹⁴. The most reliable clinical test is probably that described by Roos: clenching and unclenching the fists with the arms abducted and externally rotated, which, if positive, reproduces the symptoms¹¹. This test was positive in 25 patients in this series, a figure similar to that reported previously by this unit and others^{1,7}. Radiography of the thoracic outlet will reveal a skeletal abnormality, if present, and angiography and duplex ultrasonography can confirm arterial compression. For the majority with neurological symptoms, in whom nerve conduction testing is usually unhelpful, reliance must be placed on clinical judgement.

Many patients with mild symptoms can be treated conservatively with posture-improving exercises^{12,13}. However, those with more severe symptoms, especially if vascular in nature, should be offered surgery. There are two widely practised therapeutic options. The first is scalenectomy, which is performed via a supraclavicular route and has been reported to give results as good as those of rib excision with a lower complication rate⁷. The second is excision of the first (and cervical) rib. This can be accomplished via a supraclavicular incision⁸, through the axilla¹⁵, or by posterior thoracotomy¹⁶. The advice of Clagett¹⁶, that it is more logical to 'remove the floor (rib) than tackle the more difficult roof (scalenes)', argues strongly for rib excision. The supraclavicular route of rib removal is more fraught, takes about twice as long to perform^{8,15}, and is associated with the significant problem of

phrenic nerve paresis in about 7 per cent of cases^{5,7}. Most authorities would, therefore, now favour transaxillary excision of the first rib, reserving posterior thoracotomy for those with recurrent symptoms¹³.

In well selected patients, about 90 per cent will attain complete or partial relief of symptoms^{5,7–9}. The results of the present series compare favourably with those in the literature. Recurrent, as opposed to persistent, symptoms have been said to occur within 6 months of operation¹⁷, with an incidence^{7,9} of 2.2–5 per cent. However, two patients, from early in the previous series, have had recurrent symptoms 12 and 9 months after operation, respectively; these have had a good result from posterior excision of a remnant of first rib. So far one patient in the present series has had recurrence of symptoms, after 20 symptom-free months. The overall recurrence rate of three of 69 limbs (4 per cent) remains encouragingly low.

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Peripheral tuberculous lymphadenopathy: a review of 67 cases

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Peripheral tuberculous lymphadenopathy is the commonest form of extrapulmonary tuberculosis. Sixty-seven patients with peripheral tuberculous lymphadenopathy who presented to general surgeons and underwent lymph node biopsy between 1979 and 1989 are reviewed. Fifty-four patients (81 per cent) were of Indian subcontinent ethnic origin and 13 (19 per cent) were of white ethnic origin. The sites most commonly affected were the cervical lymph nodes. Biopsy specimens obtained by open operation were sent for microbiological examination in all but 13 cases, of whom seven were patients of white ethnic origin. Tuberculous lymphadenopathy remains an important differential diagnosis of cervical lymphadenopathy and it is essential that peripheral lymph node biopsies are examined both histologically and microbiologically.

Tuberculosis of peripheral lymph nodes is the commonest form of extrapulmonary tuberculosis^{1,2} and frequently involves the lymph nodes draining the head and neck³. In England and Wales, the majority of patients contracting tuberculosis are from the Indian subcontinent (India, Pakistan or Bangladesh). A significant proportion are also of white ethnic origin, and differences in clinical presentation have been described between the two ethnic groups⁴. This review determined the characteristics of peripheral tuberculous lymphadenopathy in patients of white and Indian subcontinent ethnic origin to determine features that may facilitate diagnosis in either group. (For simplicity, the term 'Indian' is used to identify all patients of Indian subcontinent ethnic origin.)

The population of Leicestershire 1 year before the study was estimated at 833 000, of whom 60 000 were of Indian origin⁵.

Patients and methods

A retrospective review was performed of patients with peripheral lymph node tuberculosis presenting to general surgeons within the Leicestershire group of teaching hospitals between 1979 and 1989. Patients were identified from the Hospitals Activity Analysis between 1979 and 1987, and from the Trent Regional Information System between 1987 and 1989. Data were complete except between September 1986 and April 1987, for which no information was available.

All patients underwent biopsy of a peripheral lymph node which was subjected to histological or microbiological examination. A diagnosis of tuberculous lymphadenopathy was made on identification of at least one of the following: the presence of acid-alcohol fast bacilli with Ziehl-Nielsen staining, subsequent growth in Löwenstein-Jensen medium, or the appearance of caseating granulomas on histological section^{1,6} (Figure 1).

Results

Sixty-seven patients with tuberculous lymphadenopathy were studied; their characteristics are shown in Table 1. Seventeen patients (25 per cent) had evidence of systemic symptoms, the distribution of which is shown in Table 2. The overall incidence of systemic symptoms was higher in patients of white (39 per cent) than of Indian (22 per cent) ethnic origin. This was not statistically significant. The incidence of respiratory symptoms was significantly higher in the Indian group (difference between proportions 14.8 per cent, 99 per cent confidence interval (c.i.) 2.3-27.3 per cent).

Full blood counts were performed in 59 patients (88 per cent). Microcytic hypochromic anaemia was found in

24 (41 per cent), 42 per cent in patients of white ethnic origin and 40 per cent in those of Indian origin. The total white cell count was within normal limits in all cases. Mantoux testing was performed in only 19 patients (28 per cent); 14 (74 per cent) were positive. The indications for performing this test were not clearly defined. In patients who had a sample sent for microbiological analysis, a positive culture for tuberculosis was seen in 70 per cent of those with a positive Mantoux test; in the patients with a negative Mantoux test, the culture was positive in only 50 per cent (difference between proportions 20.6 per cent, 95 per cent c.i. -36.6 to 76.6 per cent).

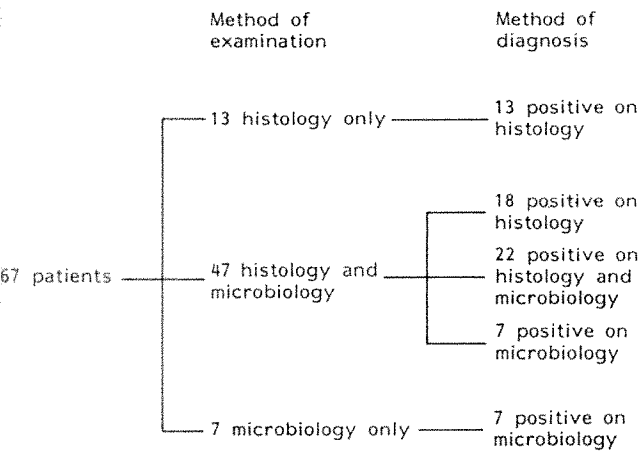


Figure 1 Flow chart showing the number of specimens examined by histology only, by microbiology only, or by both, and the method by which the diagnosis of tuberculous lymphadenopathy was made

Table 1 Patient characteristics

	Indian subcontinent group (n = 54)	White group (n = 13)
Mean age (years)	41.8	46.9
Sex ratio (M:F)	22:32	4:9
Family history*	26	1

* Difference between proportions 40.5 per cent (99 per cent confidence interval 14.5-66.4 per cent)

Table 2 Clinical details of patients

Symptom	Indian subcontinent group (n = 54)	White group (n = 13)
Weight loss	7	3
Pyrexia	7	1
Night sweats	5	2
Anorexia	4	2
Cough or sputum	8	0

Table 3 Distribution of tuberculous lymphadenopathy

Site	Indian subcontinent group (n = 54)	White group (n = 13)
Supraclavicular	16	4
Submandibular	6	0
Jugular	24	7
Axillary	6	1
Inguinal	2	1

Histological examination was positive in all patients in whom a Mantoux test was performed.

Chest radiographs were obtained in 59 patients (88 per cent), and tuberculous lesions were identified in two of white ethnic origin (18 per cent) and in 21 (44 per cent) of Indian origin (difference between proportions 25.6 per cent, 95 per cent c.i. -1.2 to 52.3 per cent). Ten radiographs showed changes of healed pulmonary tuberculosis, five showed signs of active pulmonary tuberculosis, and seven showed hilar or paratracheal lymphadenopathy.

The cervical lymph nodes were the most frequently involved site; the distribution of sites between the two ethnic groups is illustrated in Table 3.

In seven patients (10 per cent) biopsy specimens were not sent for histological examination. Histology was obtained for 60 patients (90 per cent), and in 53 (88 per cent) showed changes diagnostic of tuberculosis. Biopsy specimens were not sent for microbiological examination in 13 patients (19 per cent), of whom seven (54 per cent) were of white ethnic origin and only six (11 per cent) of Indian origin (difference between proportions 42.7 per cent, 99 per cent c.i. 5.4-80.1 per cent). Fifty-four specimens were examined by microscopy and subsequent culture: acid alcohol-fast bacilli were identified from six immediate smears (11 per cent), and culture was positive for *Mycobacterium tuberculosis* in 36 cases (67 per cent) (Figure 1).

Discussion

Tuberculous lymphadenopathy is the commonest form of extrapulmonary tuberculosis and may be encountered by the general surgeon. Previous studies have shown differences in behaviour of tuberculous lymphadenopathy between white and Indian ethnic groups⁴. This study confirms that the mean age in white patients is higher than in those of Indian origin^{7,8}.

A higher incidence of a family history for tuberculosis was seen in the Indian group, although the overall incidence was

similar to previously reported figures⁹. Cervical tuberculous lymphadenitis has previously been shown to be the commonest site for tuberculous lymphadenopathy^{2,7,8}.

The incidence of systemic symptoms was higher in the white ethnic group, and the incidence of tuberculous lesions on chest radiography higher in the Indian group, but these differences were not statistically significant.

The most significant findings relate to the mode of diagnosis. In no patient was a preoperative diagnosis made by fine needle aspiration cytology. This technique has recently been shown to have a high diagnostic accuracy¹⁰⁻¹². Histological examination and culture were positive in 88 and 67 per cent of cases, respectively, similar to previously reported figures^{7,8}. The fact that 54 per cent of white patients did not have specimens sent for microbiological examination may reflect a low index of suspicion in this group. Tuberculosis is an important differential diagnosis of cervical lymphadenopathy, and cervical lymph node biopsies should be sent for microbiological as well as histological examination.

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Subclinical injuries in lacerations to the forearm and hand

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This report describes the incidence and severity of subclinical injuries to underlying structures in lacerations to the hand and forearm. One hundred consecutive hand and forearm lacerations that penetrated the full thickness of subcutaneous tissue were studied prospectively. Lacerations were explored under either biceps or forearm tourniquets. Injuries, treatment, tourniquet time, causative agent and complications were recorded. In all, 97 patients sustained 100 lacerations. A total of 49 deep injuries were discovered, none of which was detected clinically before exploration. Of these, 33 were tendon lacerations; 21 tendons, including three flexor tendons, were repaired. Nineteen patients required treatment in a volar slab for at least 3 weeks. Five patients of 49 returning for review developed wound infection. No patient developed significant problems related to the tourniquet, which was inflated for a mean time of 4.9 min. There is a high incidence of subclinical injury in full-thickness lacerations of the forearm and hand. These should be explored under tourniquet, which should minimize complications such as wound infection and delayed tendon rupture.

The incidence of partial tendon injuries in lacerations of the hand and forearm is not known, nor is the incidence of delayed tendon rupture and malfunction. Although some authors have alluded to the presence of subclinical and missed tendon injuries, the frequency of these has not been established¹. Appreciable problems are caused by these injuries for both patient and surgeon. In the authors' experience of wound exploration, partial injuries to tendons and joint capsules are sometimes found unexpectedly without prior clinical suspicion. It was decided to study this phenomenon prospectively to establish the incidence, severity, causes and types of subclinical injury caused by lacerations to the hand and forearm.

Patients and methods

One hundred consecutive lacerations of the upper limb distal to the epicondyles and proximal to the distal interphalangeal joints were explored under tourniquet by two of the authors (B.P.McN. and J.M.). Exclusion criteria were: if the patient did not give informed consent; if the lacerations were > 12 h old; if the wound could be clearly seen not to extend below the skin or fat layer after cleansing and parting of the wound edges with finger pressure; if there was clinical evidence of disrupted nerves, tendons or ligaments or of degloving; and when the injury was a laceration or puncture wound < 5 mm in length. Three patients refused the exploration. In a few instances cuff pressure was allowed to fall slightly and oozing began but the exploration was completed satisfactorily by raising the pressure again.

Only patients presenting to the department while the authors were on duty are included in this paper. Informed consent was obtained from all patients explored. This accident and emergency department sees only patients aged ≥ 12 years; 46 000 new patients are seen each year.

Data recorded included patient demographics, length and site of laceration, whether the causative agent was sharp or blunt, the tourniquet site and time, injuries detected and treatment. The lacerating agent was defined as sharp by an affirmative answer to the question 'Would it cut you if you were to run your finger along the edge?'. The tourniquet was a standard sphygmomanometer cuff placed on the muscular part of the forearm for injuries below the wrist, or on the upper arm for forearm injuries. No cotton wool or padding was used. The forearm was used where possible because in the authors' experience of upper arm cuffs, ischaemic forearm pain requiring deflation occurs more often and more rapidly than with the forearm cuff. After injection of local anaesthetic at the site of injury, the limb was raised and the brachial artery compressed digitally until the limb was blanched – usually 1–2 min. The tourniquet was then inflated and maintained by the patient or assistant at a pressure of 180 mmHg. This figure was

chosen arbitrarily as one likely to exceed the systolic blood pressure. The surgeon then donned gloves and cleaned the wound using a solution of chlorhexidine acetate 0.05 per cent and cetrimide 0.5 per cent (Travasept 30; Baxter Healthcare, Thetford, UK). Gowns or masks were not worn by the surgeon and the wounds were examined and sutured in the same cubicles where all other minor emergencies are seen. No tissues were divided unless an injury was noted. Tendons and joints were examined in the position of injury and throughout a full range of movement. If no injury was detected the patient or assistant deflated the cuff and the skin was sutured with nylon. Detected injuries were sutured while the cuff was inflated or referred to the appropriate specialist.

All patients were instructed to attend for removal of sutures on a specified date and to return at any time if complications developed. Follow-up was in accident and emergency dressing and hand clinics or surgical outpatient departments.

Results

A total of 97 patients who sustained 100 lacerations fulfilling the study criteria were seen over a 7.5-month period. In all, 48 lacerations in 46 patients had an underlying injury detected by exploration. Table 1 shows the characteristics of these. Of 33 tendon injuries 21 (64 per cent) were repaired. Seven (21 per cent) were repaired at the time of discovery, eight (24 per cent) were brought to the accident and emergency theatre next day, three (9 per cent) were referred to general surgeons and three to plastic surgeons. The last three consisted of two partial < 50 per cent lacerations of flexor tendons both

Table 1 *Injuries detected*

Type of injury	Description	No.
Tendon	Complete division	7
Tendon	> 50% laceration	8
Tendon	< 50% laceration	18
Embedded dirt		6
Lumbrical muscle	Severed	
	Partially	2
	Completely	1
Interosseous	Partially severed	1
Muscle or fascia	Laceration	4
Fractured phalanx		1
Exposed nerve end		1
Total		49

Table 2 *Completely severed tendons*

Injured structure	Site	No. of patients
Abductor and extensor pollicis longus	Forearm	1
Both extensors of little finger	Dorsum of hand	1
Extensor of ring finger	Dorsum of hand	1
Flexor carpi ulnaris	Wrist	2

There were seven severed tendons in five patients

Table 3 *Wound infections*

Complication	No. of cases	Treatment
Cellulitis	2	Antibiotics
Purulent discharge	1	Antibiotics
Stitch abscess	1	Stitch removal
Wound oozing	1	Cleansing
Total	5	

at the base of the middle finger and one complete division of flexor digiti minimi just beyond the musculotendinous junction in the forearm. This was not detected clinically because of recruitment. Four (12 per cent) of the tendon lacerations had underlying joint capsular disruption and in two cases (6 per cent) articular cartilage was gaping. The fracture was detected in a mentally disturbed alcoholic patient who gave no history. The other seven divided tendons are described in Table 2. In the first five of them the injury was disguised by recruitment of other tendons. Both flexor carpi ulnaris injuries occurred in obese patients where the proximal end of the severed tendon could not be felt moving, and wrist flexion was performed by the other flexors of wrist and fingers.

In 75 cases the lacerating agent was sharp and 35 injuries (26 of which were tendons; 35 per cent of sharp lacerations) resulted. The 22 blunt injuries caused seven (21 per cent) tendon injuries and three others. In three cases the sharpness of the agent was not established.

Nineteen patients required a volar slab for at least 3 weeks. Indications for immobilization were at each surgeon's discretion. No patients were started on antibiotics at the time of injury.

The mean tourniquet time was 4.9 min and 3.5 min when no injury was found. The longest exploration took 11 min (a restless patient) and the longest repair and exploration combined 20 min (two extensors of the little finger). The maximum forearm operating tourniquet time was 12 min and for the biceps tourniquet 20 min.

The forearm tourniquet was used on 73 patients. The tourniquet failed in two cases through inattention (the cuffs often leaked). In one elderly patient the arteries were sclerosed and the forearm tourniquet failed although it was possible to see the necessary structures with some difficulty. Three patients refused the exploration and were excluded. Underlying structures were not seen in one palmar laceration because of the narrow wound aperture and dense palmar fat. An assistant was required to use the cuff on only a few occasions; the patient was usually able to control the pressure satisfactorily. Bleeding after release of the tourniquet was brisk but active elevation of the arm by the patient and compression of the bleeding part brought haemostasis within a few minutes. No patient required re-exploration or compression bandaging and all were discharged home, some returning for surgery next day. There was no episode of delayed haemorrhage. All patients who consented tolerated the procedure well; some complained of mild discomfort or paraesthesia but none required or requested termination of the procedure.

Despite all requests and instructions only 49 patients (51 per cent) returned for removal of sutures and examination. Complications are listed in Table 3.

Both cases of cellulitis were in patients with no underlying injury whose wounds were deeply contaminated. The other three infections arose in lacerations with small tendon injuries repaired primarily in the accident and emergency department. No infections occurred in those with skin injuries only or who underwent surgery outside the accident and emergency department. All infections resolved with prescribed therapy, although one patient did not return for review.

Discussion

There is an appreciable incidence of subclinical injuries in full-thickness lacerations of the forearm and hand. Some of the tendon injuries could have been left unrepaired with no loss of function, for example division of the flexor carpi ulnaris, and some of the partial lacerations may well have healed spontaneously. Unfortunately, it is not possible to predict which tendon lacerations will subsequently rupture. Nineteen patients were treated with volar slabs requiring several weeks of splintage and rehabilitation with impaired occupational, domestic and leisure activity. It is important to achieve a balance between conservative and active management to avoid possible consequences of misdiagnosis, such as delayed tendon rupture, capsulitis, septic arthritis, tendon subluxation² and Boutonnière deformity.

Wounds requiring exploration according to the criteria used in this study were surprisingly uncommon. In many wounds the depth was often apparent when the edges were parted. In our experience such wounds are seen at a rate of ten patients per month for a casualty officer on a 50-h week.

This method probably adds time to patient treatment by exploration under tourniquet and it requires a level of surgical experience that junior casualty officers may initially lack. However, the benefits of early detection and appropriate treatment are self-evident.

The use of the forearm tourniquet has not been described previously in the literature. Some clinicians have suggested that nerves might be more vulnerable to injury by the tourniquet in the forearm rather than in the arm. Animal experiments suggest that it may take 6 h of ischaemia to produce a permanent neurological dysfunction and 1 h to produce temporary impairment in the peroneal nerve³. High pressures (> 500 mmHg) have produced neurological injury in humans⁴. We feel that the method described here is safe in the conscious patient with a short tourniquet time when the patient can alert the doctor to paraesthesia, and the function of median, ulnar and radial nerves can easily be assessed during and after operation.

The wound infection rate reported here is not accurate because of the incomplete follow-up. This is common in inner city accident and emergency departments where patients comply poorly with requests for review⁵⁻⁷. Assuming the infections seen on review were the only ones which developed, they constituted a 5 per cent overall infection rate and 10 per cent of those who returned, which is similar to the lowest reported figures⁶⁻⁹ of 4.9-17.5 per cent. However, this group was selected and was also biased towards high infection rates because the wounds were deep and sometimes dirty. Operator experience might also be greater than in other studies as no senior house officers were involved. The methods used should, in theory, reduce infection rates unless primary tendon repair predisposes to wound infection. The absence of wound infection in those with only skin injuries suggests that the method may reduce infection rates if there is no tendon repair or contamination.

It is concluded that subclinical injuries occur in nearly half of lacerations to the forearm and hand where the wound extends below the subcutaneous tissue. One-third of all injuries were tendon injuries and 64 per cent of these were repaired, three of them being to flexor tendons. A safe, simple and effective tourniquet method is described. Although the follow-up rate was low, infection rates were acceptable and no infections were

noted in those who sustained skin lacerations only. This method of assessment may reduce wound infection rates, and should reduce the late complications of missed tendon, joint capsule and muscle injuries.

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Announcement

Association of Surgeons in Training

Membership of the Association is open to trainees in all the surgical specialties. Applicants should be at least 2 years after Fellowship. It is anticipated that at this year's AGM the constitution will be amended to allow all graduates of the Clinical Surgery in General exam to apply for membership. The Association represents the views of members on all matters relevant to surgical training and has representatives on most of the committees and boards that administer British surgery. Membership is free. If you are not a member please contact the Secretary, Bob Baigrie, 7 Coverley Road, Oxford OX3 7ET, for details of membership, the AGM and the name of your local representative. The next AGM will be held on 23–24 September 1992 in conjunction with the Autumn meeting of the Association of Surgeons of Great Britain and Ireland in Dublin.

R. J. Baigrie

Parotid disease and human immunodeficiency virus infection in Zambia

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Among the salivary glands the parotid is unusual in that it contains lymphoid tissue within its capsule. The focus of infection with human immunodeficiency virus (HIV) is the lymphatic system and this results in a specific HIV-related pathology in the parotid. This 2-year surgical audit of parotid disease in HIV-infected patients in Lusaka shows patients presenting with parotid lymphadenopathy, bilateral diffuse parotid enlargement and parotid lymphoepithelial cysts. Clinical presentation and management are discussed.

Human immunodeficiency virus (HIV)-related disease of the parotid gland presenting in the USA has recently been reported¹⁻⁸. This study reviewed HIV-related parotid disease presenting over a 2-year period to a surgical unit in a central African teaching hospital where HIV-1 infection is common⁹.

Of the salivary glands the parotid gland is unusual in including lymphoid tissue within its capsule resulting from intermingling during development of the protoparotid epithelial buds with lymphocytic rich stroma before the parotid capsule is formed^{10,11}. Intraparotid lymph nodes and unencapsulated lymphoid tissue are normally found in the substance of the parotid. Periparotid lymph nodes are in intimate contact with the capsule of the parotid gland and rests of parotid epithelium may be found in intraparotid and periparotid lymph nodes^{12,13}.

Infection by HIV is accompanied by a characteristic follicular hyperplasia of lymphoid tissue which can be recognized histologically as primary HIV lymphadenopathy^{14,15} and presents clinically as persistent generalized lymphadenopathy. Subsequent opportunist infections and HIV-related neoplasia^{16,17} can result in secondary HIV lymphadenopathy. Parotid lymph nodes reflect these HIV-related changes.

Diffuse enlargement of the parotid glands, sometimes with sicca symptoms¹⁸⁻²¹ and parotid lymphoepithelial cysts²⁻⁷ are recognized further manifestations of HIV infection.

Patients and methods

All patients who presented to one general surgical unit of the University Teaching Hospital, Lusaka, Zambia, over a 2-year period (1989-1991) were studied in a prospective clinicopathological study of lymphadenopathy presenting for biopsy. The diagnosis of HIV infection was made clinically and with a single serological test²² (Wellcozyme recombinant enzyme-linked immunosorbent assay kit; Wellcome Diagnostics, Dartford, UK), as is common in eastern central Africa.

Results

The presentation of HIV-related disease in the parotid area is shown in Table 1.

Parotid lymphadenopathy

Parotid lymphadenopathy was defined as palpable preauricular nodes, and present in 69 of 261 HIV-seropositive patients with generalized lymphadenopathy (defined as the presence of palpable lymph nodes in two or more non-contiguous extrainguinal sites) who underwent lymph node biopsy during the 2-year period. The nodes measured 0.5-3 cm in their greatest dimension and were occasionally the presenting complaint. In all but one patient, biopsy of a node other than the parotid provided the histological diagnosis. The palpable parotid lymph nodes shared the clinical character of the other nodes.

Bilateral, diffuse parotid enlargement

Nine patients presented with bilateral parotid enlargement that was smooth, sometimes slightly lobulated, and generally symmetrical (Figure 1). The consistency of the parotid was noted in five patients: it was firm in three and soft in two. Eight of the patients had generalized lymphadenopathy caused by primary HIV lymphadenopathy in five, Kaposi's disease²³ in two and tuberculous lymphadenitis in one. Two patients had symptoms of xerostomia; none had eye symptoms. Six patients underwent a small preauricular excision biopsy of the parotid under local anaesthesia without complication; in five of these the parotid showed destruction and lymphocytic infiltration with, in some cases, myoepithelial islands and microcysts. Diagnostic material was not available in the sixth case.

Parotid lymphoepithelial cysts

Four patients presented with multiple cystic parotid lesions (three bilateral and one unilateral) (Figure 2) of between 1 month and 4 years' duration. The size of the cysts was 0.5-4 cm in diameter. The cysts were thin walled, externally smooth with a cobblestone appearance on the inner surface. They contained yellow, brown or green opalescent fluid. In one patient both parotid glands increased dramatically in size during the week before surgery, and at operation multiple small, intraparotid abscesses were found in addition to the cysts.

One patient has undergone bilateral superficial parotidectomy, one enucleation of the cysts, and the patient with infection an open parotid biopsy. The fourth patient, with multiple cysts confirmed by ultrasonography, refused surgery and has been under review for 18 months, during which time there has been a gradual increase in size of the cysts without a deterioration in general condition or appearance of other HIV-related signs.

Histologically the cysts were lined with multilayered cuboidal epithelium showing varying degrees of squamous metaplasia. The cyst wall contained small lobulations caused by aggregates of lymphoid cells. In the surrounding parotid parenchyma there was lymphocytic infiltration, evidence of parotid epithelial destruction, myoepithelial islands and microscopic cysts bearing the same histological features as the macroscopic cysts.

Extraparotid lymphoepithelial cysts

Unilateral extraparotid lymphoepithelial cysts of diameter 2 and 3 cm were removed from the jugulodigastric area of two patients, both of whom had generalized lymphadenopathy and attended for biopsy of what was taken clinically to be an asymmetric node. In neither patient was parotid enlargement observed. At surgery the cyst in both patients was associated with a lymph node close to the parotid gland. Histological

Table 1 Human immunodeficiency virus-related parotid disease presenting in Lusaka in the period 1989–1991

Clinical presentation	No. of patients	Age (years)	Sex ratio (M:F)	Generalized lymphadenopathy	Weight loss
Parotid lymphadenopathy	69	18–55	34:35	69	26
Tuberculous lymphadenitis	32				
Primary HIV lymphadenopathy	22				
Kaposi's disease*	11				
High-grade B cell lymphoma	1				
Castleman's disease†	1				
Non-specific lymphadenitis	2				
Bilateral, diffuse parotid enlargement	9	19–61	3:6	8	4
Parotid lymphoepithelial cysts	4	39–50	1:3	1	1
Extraparotid lymphoepithelial cysts	2	27, 33	0:2	2	1
Parotid fistula	1	30	1:0	1	1
Parotid abscess	1	31	1:0	1	0

*See reference 23; †an angiofollicular lymphadenopathy²⁴

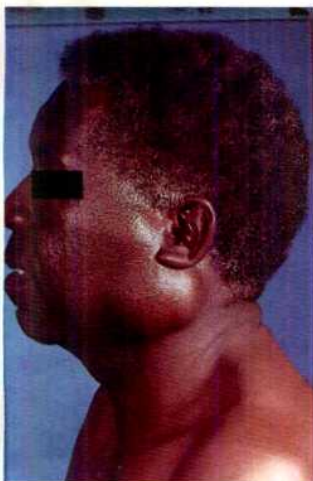
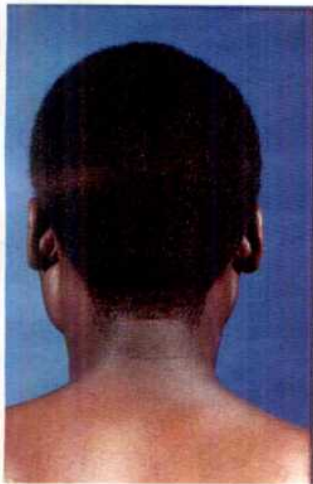


Figure 2 Lateral view of a patient with bilateral parotid lymphoepithelial cysts

study demonstrated a lymphoepithelial cyst arising from a hyperplastic lymph node containing scattered islands of parotid epithelium.

Parotid fistula

One patient with a previous history of oral candidosis and pulmonary tuberculosis presented with a spontaneous fistula of 5 months' duration, continuously draining clear fluid and

opening posteroinferiorly to the left ear lobe. A well formed fistular track, 0.5 cm long and surrounded by fibrosis, was excised at surgery with a wedge of parotid attached. Histological examination showed an epidermal lined fistula and non-specific inflammation of the parotid.

Parotid disease that was not HIV related managed by the unit during the 2-year study included: papillary carcinoma (one patient); pleomorphic adenoma (one patient); seven patients with parotid lymph nodes from 25 with generalized lymphadenopathy from HIV-unrelated tuberculous lymphadenitis or lymphoma; and three patients with diffuse bilateral parotid enlargement (one from cachexia, one postoperative pneumoparotid swelling²⁵, and one patient with idiopathic swelling and a normal biopsy).

Discussion

HIV infection produces new disease entities in the parotid gland. In a number of patients parotid disease may be the only clinical sign of HIV infection at the time of presentation. In some patients with generalized lymphadenopathy parotid lymphadenopathy may be the presenting complaint.

The causes of parotid lymphadenopathy in this study reflect the causes of lymphadenopathy prevailing in Zambia: HIV-related tuberculous lymphadenitis, primary HIV lymphadenopathy, Kaposi's disease and the occasional lymphoma.

A syndrome similar to Sjögren's disease was described early in the HIV epidemic²⁶, and recently an autoimmune, antisalivary antibody-negative parotiditis has been defined in HIV-infected individuals who carry the human leucocyte antigen-DR5 major histocompatibility complex class^{20,21}. Sicca-negative parotid enlargement is also described¹⁸. In this study only two patients with diffuse bilateral parotid enlargement had sicca symptoms on direct questioning. It is therefore possible that there are two populations of patients with diffuse parotid enlargement, one representing an autoimmune lymphocytic infiltration of the gland and the other representing HIV-related primary hyperplasia of intraparotid lymphoid tissue. Another HIV-related cause of diffuse parotid enlargement is a diffuse lymphoma¹⁸.

Before the HIV epidemic parotid lymphoepithelial cysts were rare⁶, but they are now recognized as part of the spectrum of parotid involvement in HIV infection^{2–5}. They probably result from HIV-related hyperplasia of intraparotid lymph nodes harbouring parotid epithelium⁷. Extraparotid lymphoepithelial cysts in relation to HIV infection have not been described before and support their origin from rests of parotid epithelium within lymph nodes.

The management of parotid swelling in HIV disease has yet to be standardized. Fine needle aspiration cytology can be diagnostic of HIV-related parotid swelling and lymphadenopathy^{2,5,8,27}. If, as in Zambia, there is no established cytology

service, diagnosis in a patient whose parotid lymphadenopathy is part of a generalized lymphadenopathy may be achieved by biopsy of the most enlarged or accessible node. In a patient with simple, diffuse, symmetrical parotid enlargement, positive HIV serology may allow a diagnosis of HIV-related parotid enlargement if associated with appropriate cytology. Where doubt persists a simple preauricular wedge excision biopsy can be carried out without morbidity.

During the early stages of the recognition of HIV-associated lymphoepithelial cysts, most reports advocated superficial parotidectomy^{2,4,5} but, in view of the reduced life expectancy of patients with HIV infection²⁸ and the morbidity of parotidectomy²⁹, conservative management may be more appropriate. Repeated aspiration of lymphoepithelial cysts has been advocated⁸, but is often difficult because of the multiplicity of cysts. Alternatively, simple enucleation of cysts, once the course of the facial nerve has been safely identified, may be carried out. In the one patient in this study who has undergone this procedure, there has been no recurrence at 6 months. The cysts observed in HIV disease are usually multiple with normal intervening parotid tissue and therefore easily distinguished at surgery from solitary cysts, which are commonly associated with malignancy and for which a partial parotidectomy is indicated³⁰.

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Breast cancer in Nigerian women

A combined retrospective (1971-1980) and prospective (1981-1990) study of the epidemiology, clinical characteristics and pathology of breast cancer in a black African population was carried out. There were 1946 biopsy-proven cases, with a rate frequency of 33.6 per 100 000 patients per year. The age range was 14-96 years but 70 per cent of patients were between 26 and 50 years old. The cumulative frequency of cancer was 0.8 per cent at age <20 years and 3.3 per cent at age <25 years; the peak age range for disease was 36-45 years. Of 1842 evaluable patients, 17.2 per cent presented with stages I or II cancer and 73.8 per cent with stage III disease. The dominant histopathological type was infiltrating ductal cancer (49.2 per cent), followed by undifferentiated anaplastic carcinoma (33.3 per cent). Burkitt's lymphoma occurred in five patients and developed concurrently and rapidly during lactation in four. The prospective study did not demonstrate that age at menarche or first full-term pregnancy, duration of breast feeding or parity were risk factors in black women.

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Although it is the most common malignancy afflicting women in much of Europe and North America^{1,2}, breast cancer has been considered rare in populations indigenous to the African tropics^{3,4}. World Health Organization reports¹, International Agency of Research on Cancer bulletins⁵ and surveys in seven countries of tropical Africa⁶⁻¹¹ have shown breast cancer incidence rates up to 1976 never exceeding 15.3 per 100 000 population per year. Attempts to ascribe this low level to peculiar host and environmental factors (including genetic, hormonal, menstrual, viral and dietary) remain unconfirmed.

In 1980, at the University College Hospital, Ibadan, a breast diseases study project was started at the surgical oncology unit of the department of surgery. Its aim was to document the pattern of the disease in one region of the African tropics that was undergoing rapid environmental, population, economic and social change.

Patients and methods

Two groups of patients (group 1, retrospective; group 2, prospective) were studied collectively to determine the epidemiological characteristics, clinical presentation and pathology of disease as it occurs in black African women.

Group 1: retrospective study 1971-1980

This group of 637 patients had biopsy-proven breast cancer and information was available on the age, histological type and stage of disease in 623 patients. In 422 of these, however, only the symptoms and signs were documented.

Group 2: prospective study 1981-1990

In all, 1309 patients were entered into the project. Diagnosis was based on history and clinical examination and confirmed by open biopsy.

Patients were seen at the early part of the study against a background of publicity highlighting the dangers of breast cancer and encouraging self-examination in women of all ages. Details of possible predisposing factors, menstrual history, age at first full-term pregnancy, parity, breast feeding history, family history of mammary, uterine or ovarian malignancy, and the use of contraceptive medication were all explored and recorded. The place of residence, occupation, diet and dietary preferences and awareness of the dangers of breast cancer were determined.

Measurements of height and weight were made and an assessment of the degree of obesity computed using the Quetelet index¹². Patients were followed for between 6 weeks and 9.2 years with a mean (s.d.) follow-up of 3.8 (1.7) years. Documentation was incomplete for 52 patients, and 38 were lost to follow-up, leaving 1219 evaluable cases. With 623 patients in the retrospective group, a total of 1842 patients were available for analysis. A group of 460 healthy women, including

nurses, paramedical workers and healthy visitors to the hospital, were processed and matched as group controls for the study population.

Statistical analysis

Values were expressed as mean (s.d.) where appropriate and statistical analysis conducted using Student's *t* test and the Mann-Whitney *U* test.

Results

Epidemiological characteristics

Annual incidence and rate frequency. The mean annual incidence during the first half of the study period was 63.7, increasing to 130.9 during the second half of the study period. The pattern of annual incidence over the 20-year period and the successive 5-year incidence profiles (Figures 1 and 2) show a rising trend.

Based on the 1946 patients with the histological diagnosis and a female at-risk population of 0.29 million for the catchment area served by the hospital during the middle of the study period, the rate frequency per 100 000 of the population was 33.6 per annum.

Age distribution. From age 26 the incidence rose steeply, reaching a peak between 36 and 45 years, a period when the majority of women had finished having children. A smaller secondary peak between 56 and 65 years was noticeable (Figure 3). The mean age was 48 years. The cumulative frequency was 0.8 per cent at <20 years and 3.3 per cent at <25 years.

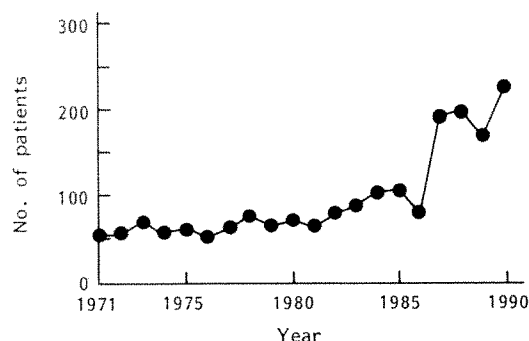


Figure 1 Annual incidence of breast cancer 1971-1990

Personal, social and dietary history. Seventy-one patients (5.8 per cent) were of social class I and 159 (13.0 per cent) class II. The majority of patients were rural and semiurban dwellers engaged in petty trading in a variety of food products such as rice, beans, pepper, fruits and vegetables.

Measurements of height showed a range of 139–177 cm (mean(s.d.) 165.7(10.2) cm *versus* control 167.2(10.6) cm, $P > 0.05$). Measurements of weight showed a range of 33–96 kg (mean(s.d.) 60.2(4.2) kg *versus* controls 65.1(3.8) kg, $P > 0.05$). The Quetelet index calculated for the study population and the age-matched controls showed that approximately 58 and 61 per cent respectively of each group were obese. This difference was not statistically significant.

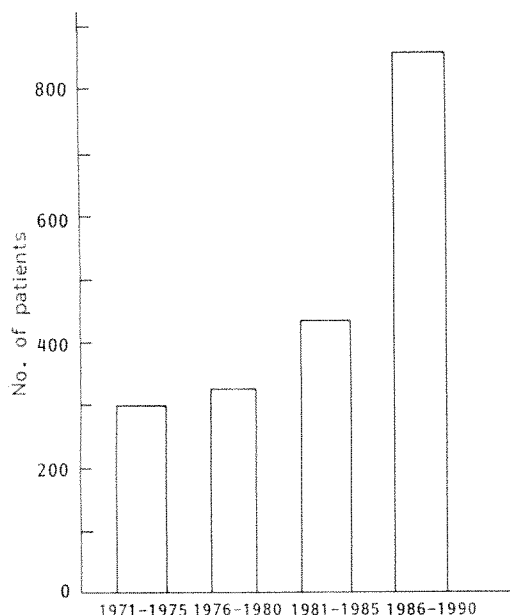
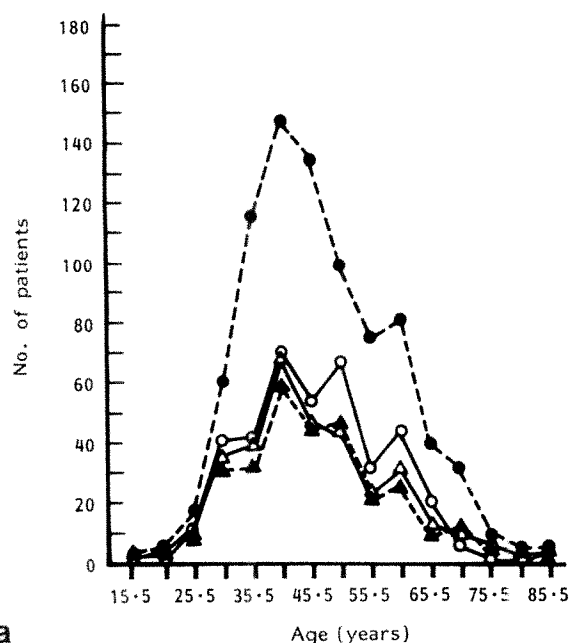
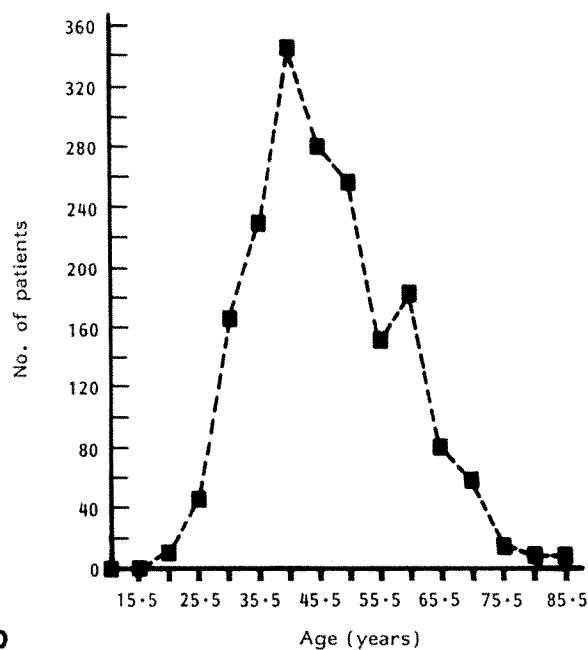


Figure 2 Incidence of breast cancer during the four 5-year periods 1971–1990



a



b

Figure 3 **a** Age distribution of breast cancer for each 5-year period: $\blacktriangle$, 1971–1975 ($n = 303$); $\triangle$, 1976–1980 ($n = 334$); $\circ$, 1981–1985 ($n = 445$); $\bullet$, 1986–1990 ($n = 864$). **b** Composite distribution for all 1946 patients (1971–1990)

The bulky diet common to most of black Africa consisted of carbohydrates (60–70 per cent), proteins (15–20 per cent), vegetable fats (10–15 per cent) and others (1–5 per cent). With the exception of 22 patients who admitted to the use of tobacco as cigarettes (nine cases) and snuff deposited on the tongue (13 cases), the majority were non-users. Alcohol in the form of spirits (24 patients) and beer (76 patients) was taken only occasionally.

Breast disease awareness. Although breast diseases, especially abscesses, were well known to most patients, the pathology and significance of breast cancer was unfamiliar to the majority of the study population. Two-thirds had never seen the disease before; 67 (5.5 per cent) had observed it in a neighbour, friend or distant relation, but 524 patients (43.0 per cent) had harboured an increasingly painful breast lump and become alarmed by the onset of a bloody nipple discharge or of ulceration.

Fifty-nine patients (4.8 per cent) discovered the tumour on self-examination after seeing publicity. Twenty-two others (1.8 per cent) with ulcerated and fungating breast tumours had been forced from their homes by their families because of the odour of their discharging breast ulcers. One hundred and ninety-six patients (16.1 per cent) had been referred from other clinics and 757 patients (62.1 per cent) came from outside referrals.

Menstrual and obstetric history. Three hundred and twenty-nine patients (27.0 per cent) were uncertain of their menarche age. Among the remainder, this varied from 12 (5.7 per cent) to 20 (8.6 per cent) years with a mean(s.d.) of 15.8(0.5) years. More than half (51.4 per cent), however, were between 15 and 16 years. The mean(s.d.) age at menarche for controls was 15.2(0.3) years ($P > 0.05$).

The age at first full-term pregnancy ranged from 15 (3.3 per cent) to 37 (1.7 per cent) years with a peak between 19 and 20 years (30 per cent). A secondary peak between 25 and 26 years (20 per cent) was also noted. The mean(s.d.) age was 23(1.0) years compared with 21.6(0.7) years for controls ($P > 0.05$). Sixteen per cent of patients were uncertain of their age at first pregnancy.

Table 1 Symptoms and signs of breast cancer

	1971-1980 (n = 422)	1981-1990 (n = 1219)
Breast mass	422 (100)	1219 (100)
Pain	346 (82.0)	945 (77.5)
Peau d'orange	292 (69.2)	780 (64.0)
Ulceration	173 (41.0)	411 (33.7)
Fixity to chest	110 (26.1)	301 (24.7)
Nipple retraction	51 (12.1)	165 (13.5)
Nipple ulceration	66 (15.6)	123 (10.1)
Nipple discharge	0 (0)	123 (10.1)
Arm oedema	27 (6.4)	27 (2.2)

Values in parentheses are percentages

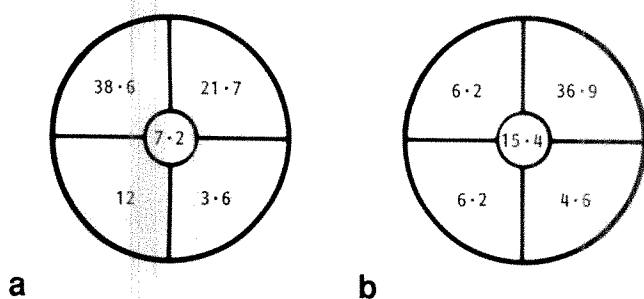


Figure 4 Location of tumour in 1027 patients. Values are percentages. **a** Right breast (whole breast affected in 16.9 per cent); **b** left breast (whole breast affected in 30.7 per cent)

Parity varied from none (5.4 per cent) to 11 (1.4 per cent) with one-third of patients having borne four or five children. The mean(s.d.) number was 6.4(0.4) versus 5.9(0.2) for controls ($P > 0.05$). No information was available for 14 per cent of patients. Breast feeding, occurring in 96 per cent of patients, ranged in duration from 2 to 36 months, with a mean(s.d.) of 17.5(2.4) months versus 18.2(2.5) months in controls. In 11 patients there was a family history of cancer in the mother: uterine (six), ovarian (two) and breast (three). In 13 others, a close relation, a sister or an aunt was known to have suffered a malignant condition involving the breast (five), stomach (two), uterine cervix (two), ovaries (two), skin (one) or nasopharynx (one). Only 28 women (3.5 per cent) of 809 on whom information was available admitted to the use of contraceptive pills. No patient admitted to a previous history of mammary dysplasia.

Clinical characteristics

Duration of symptoms. Only 3 per cent of patients gave a history of symptoms of < 1 month; 25 per cent gave a history of ≤ 3 months and 51.5 per cent of ≤ 6 months. In 17.9 per cent of patients, the disease had been present for between 7 and 24 months, and 7.3 per cent had had symptoms for > 25 months. In 284 patients (23.3 per cent) the duration of the disease was doubtful. The mean(s.d.) delay was 10.9(2.7) months (range 2 weeks to 38 months). For 422 patients seen between 1971 and 1980, the mean(s.d.) duration of disease was 16.6(1.9) months. Symptoms and signs are shown in Table 1.

Tumour location and size. The right breast harboured the tumour in 53 per cent of cases compared with 42 per cent for the left side. Bilateral disease occurred in 5 per cent of patients, in whom the tumour involved the two breasts diffusely in three-quarters (Figure 4).

The tumour varied in size between 1.3 cm (0.3 per cent) in a superficial nearly ulcerated dimple and 23 cm (3.4 per cent); the mean(s.d.) size was 6.5(1.2) cm. Burkitt's lymphoma of the breast accounted for the largest tumours recorded.

Nodal status, metastases and disease stage. A total of 184 patients (15.1 per cent) had one to three palpable ipsilateral lymph nodes, which were matted or fixed at presentation. In 666 patients (54.6 per cent) the affected lymph nodes were estimated at four or more in number, matted, globular, poorly mobile or fixed. In 22.7 per cent of cases, the contralateral axillary glands were enlarged but mobile. Twenty-one patients (1.7 per cent) had clinically uninvolved ipsilateral axillae. Seven mastectomy specimens (0.6 per cent) were reported free of nodal involvement; 82 per cent had lymph node involvement.

Metastases arising from the breast were found at presentation in 9 per cent of cases. They were localized to the pleura with effusions in 2.8 per cent and the lungs in 1.9 per cent (Table 2).

Based on the Manchester tumour node metastasis (TNM) system for clinical staging, 17.2 per cent of the patients were stage I ($T_1N_0M_0$) and stage II ($T_{1/2}N_1M_0$). The largest group, 73.8 per cent, were stage III ($T_{2/3}N_2M_0$) who, together with stage IV patients ($T_{2-4}N_2M_1$), accounted for 82.8 per cent of all cases.

Pathological features: tumour histopathology

In the 1842 evaluable patients with breast cancer (1971-1990), histopathological definition of tumour type showed infiltrating

Table 2 Metastatic sites in breast cancer

Site	No. at presentation
Pleura	34 (2.8)
Lungs	23 (1.9)
Vertebra	19 (1.6)
Lumbosacral	10 (0.8)
Thoracolumbar	4 (0.3)
Sacroiliac	3 (0.2)
Pelvis	2 (0.2)
Liver	17 (1.4)
Brain	6 (0.5)
Orbit	4 (0.3)
Ribs	3 (0.2)
Ovaries	2 (0.2)
Peritoneum	1 (0.1)
Total	109 (8.9)

Values in parentheses are percentages of the total 1219 cases

Table 3 Histopathological types of breast cancer

	No.
Type I: non-infiltrating	
Paget's disease with intraductal carcinoma	2 (0.1)
Moderately well differentiated adenocarcinoma	37 (2.0)
Type II: infiltrating	
Paget's disease with infiltrating carcinoma	21 (1.1)
Ductal carcinoma	
Infiltrating ductal carcinoma	907 (49.2)
Medullary carcinoma	108 (5.9)
Papillary carcinoma	42 (2.3)
Mucinous (colloid) carcinoma	27 (1.5)
Comedocarcinoma	8 (0.4)
Lobular carcinoma (infiltrating)	52 (2.8)
Infiltrating anaplastic carcinoma	614 (33.3)
Type III: other neoplasms	
Lymphoma	9 (0.5)
Malignant	4
Burkitt's	5
Sarcoma	8 (0.4)
Fibrosarcoma	6
Liposarcoma	2
Cystosarcoma phylloides (malignant)	7 (0.4)
Total	1842 (100)

Values in parentheses are percentages

ductal carcinoma (49.2 per cent) as the most common type (Table 3). Malignant lymphoma of the breast was found in four patients aged 27, 30, 32 and 60 years, and the Burkitt type in five patients aged 14, 18, 27, 30 and 35 years. Characteristically the Burkitt masses were bilateral (four patients) with the breasts replaced by multiple bosselations, some of which had led to skin necrosis and ulceration. Four of the five patients with Burkitt's lymphoma (aged 18, 27, 30 and 35) were lactating at the time of presentation.

Discussion

Although it has been known¹³⁻¹⁵ to much of Europe and North America for over 100 years, breast cancer is still a rare disease in much of black Africa. In several areas of Nigeria there is no local word for, or extant description of, a fatal breast disease afflicting women. Patients reporting their experience with the condition often have to be assisted by direct questioning with respect to symptoms and signs.

The incidence as reported by early investigators in tropical Africa⁵ was low, with age-related frequency levels varying between 13.8 and 15.3 per 100 000. These reports were based on small numbers of patients studied retrospectively over short periods of time. There was no assessment of the prevailing attitudes and awareness of the population towards cancer in women, especially with respect to reporting methods, social and cultural inhibitions in describing female body parts, treatment preferences (including the possible loss of a breast) compliance with a long period of follow-up, and the possibility of death. The present study has shown a frequency of 33.6 per 100 000 patients per year compared with a previous 15.3, an increase that is not matched by facilities and resources for adequate treatment.

The 1978 rise occurred because of a low-level campaign and counselling mounted by social workers informing patients that the disease was treatable and that treatment at the hospital was free. The 1982 rise coincided with a campaign on television and radio by the Nigerian Cancer Society on the need for breast self-examination. A slight reduction occurred in 1986 because of severe economic conditions in the country at that time. It was compensated for in 1987 by the large return to the hospitals with the start of radiotherapy services at the University College Hospital, Ibadan. These influences, however, do not explain the strong upward trend during the past 10 years.

The age distribution shows a gradual rise from 15.5 to 30.5 years, accounting for 12 per cent of cases. This is in contrast to the 1.5 per cent for caucasians in this age group documented by Haagensen¹⁶. The Nigerian peak is 10-15 years earlier than the peak age range for caucasian women^{16,17}. A smaller secondary peak (56-65 years) gives the age distribution a unique African type profile, which is very different from the Western type of curve¹⁸ and others¹⁹. Postmenopausal patients accounted for only 20 per cent of cases, in contrast to caucasians where this group contributes two-thirds of all cases^{16,19,20}. There is no evidence that older women are not presenting⁶. Although a comparison between the total female age distribution between Nigeria and Western Europe is likely to show fewer older women in Nigeria, the relative proportions with the disease should not be different. A low cumulative prevalence of 0.8 per cent at <20 years and 3.3 per cent at <25 years contrasts with the overwhelming predominance of fibroadenoma in this age group²¹. The rarity of breast cancer in caucasian women <25 years of age is unexplained^{16,19,20}.

Menstrual and obstetric variations have been suggested as contributing to risk of breast cancer^{16,20,22-24}. Results of the present study suggest that, in black women, these menstrual and obstetric factors do not contribute to risk of breast cancer.

The role of obesity and diet²⁵, the contraceptive pill²⁶ and cigarette smoking^{27,28} in the development of breast cancer remain unclear. Although more than half of the age-standardized study population were obese according to their Quetelet index, the equivalent data for normal controls were

no different. A greater number of individuals have now added refined vegetable oils to their diet, but there is no evidence that patients with breast cancer did this any more than controls.

The late presentation of a majority of patients (mean(s.d.) 10.9(2.7) months) was shown by the large numbers presenting with peau d'orange (64.0 per cent), ulceration (33.7 per cent) or solid fixation to the chest wall (24.7 per cent), and by those with nodal disease that was matted or fixed and affecting more than three nodes (54.6 per cent). These groups together accounted for up to 83 per cent of cases. In contrast, caucasian women present after a mean delay^{16,29,30} of 4-6 months.

The histopathological types occurring in black women are similar to those found among caucasian women, but the proportions differ^{16,31,32}. Although the majority of patients in this study presented with infiltrating ductal carcinoma with much stromal reaction (49.2 per cent), infiltrating poorly differentiated anaplastic tumours accounted for one-third of cases. The rare Burkitt's lymphoma occurred in five adult women, four of whom presented with bilateral disease and were lactating at the time. The significance of lactation in association with Burkitt's lymphoma of the breast is not known.

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Case report

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Successful splenectomy for lymphoproliferative disease in octogenarians

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Splenectomy has an established place in the management of massive splenomegaly causing anaemia and thrombocytopenia. In most reported series the upper age limit is approximately 70-75 years. The cases are reported of two octogenarians with chronic polymphocytic leukaemia and hypersplenism. Removal of a massive spleen in these patients proved well worth while.

Case reports

Patient 1

An 80-year-old man, who had previously been fit and independent but who was at the time receiving monthly chlorambucil therapy, became disabled by discomfort, anorexia and ankle oedema. The spleen was massively enlarged (weighing 4 kg) and a thoracoabdominal incision was required for its removal because of dense adhesions to the diaphragm. The platelet count was $18 \times 10^9 \text{ l}^{-1}$ before operation and $202 \times 10^9 \text{ l}^{-1}$ on day 4 afterwards. Postoperative bronchopneumonia responded to amoxycillin. After convalescence the patient was discharged home on day 22. Four weeks later he was readmitted with increasing breathlessness caused by multiple pulmonary emboli; the platelet count was $269 \times 10^9 \text{ l}^{-1}$. The patient was successfully treated with heparin and subsequent warfarin. His general health improved greatly and he required no further treatment for leukaemia for 2 years.

Patient 2

An 84-year-old man, who had been well until recently, deteriorated until he required blood transfusion every 3 weeks plus platelet transfusion to control frequent epistaxis. He developed cellulitis of the arm and nasal impetigo secondary to neutropenia. Although bone marrow function was impaired by leukaemic replacement, his massive splenomegaly contributed to the pancytopenia. The preoperative haemoglobin concentration was 4 g dl^{-1} , platelet count $32 \times 10^9 \text{ l}^{-1}$ and white cell count $67 \times 10^9 \text{ l}^{-1}$, predominantly polymphocytes. Perioperative transfusions of a total of 20 units platelet concentrate and 5 units red cell concentrate were given to permit safe removal of

his 2.2-kg spleen, plus a further 24 units after operation to day 5. The patient was discharged home on day 12. The neutropenia resolved early, the anaemia and thrombocytopenia more slowly and incompletely because of bone marrow failure. He required two small blood transfusions and no further platelet transfusions in the 5 months after discharge.

Discussion

Reviewing an extensive series of splenectomies in 1987, Dawson and colleagues¹ discussed the many indications for operation, the commonest being bulk symptoms and hypersplenism. Potential benefit is greater in lymphoma and lymphocytic leukaemia than in myeloid disease, where organomegaly suggests a terminal condition. Even patients with late lymphocytic disease may benefit^{2,3}; predictive red cell tests often underestimate the response². Several series specify that age and sex have no influence on prognosis. In comparable procedures, surgical results have been no worse in selected patients over the age of 80 years than in younger groups⁴. Late infection following splenectomy poses fewer problems when longevity is unlikely and may in any case reflect the underlying disorder and immunosuppressive therapy rather than splenectomy^{1,5}.

It is proposed that there should be no upper age limit for splenectomy in appropriate patients with lymphoproliferative disorders, provided the haematologist can be closely involved in perioperative management. Adler *et al.*² have claimed that this involvement reduces the mortality rate at all ages.

Patient and surgeon alike must be aware of the hazards and the uncertainty of outcome, but if the procedure is successful, not only may survival and quality of life be improved, but health service costs may be reduced by avoidance of expensive transfusions².

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Managing swabs in the operating theatre: a new method

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The swab count has traditionally used a swab rack. A new alternative 'bag' method involves placing used swabs in batches of five into plastic bags which are sealed and stored in a bin. A randomized prospective study was carried out to compare these two methods. Twenty consecutive ear, nose and throat cases were randomized to rack or bag collection. Swab-related activities were divided into three categories and analysed by formal time-and-motion criteria. Blood contamination of operating theatre and circulating personnel was recorded. The time involved in all three swab-related activities was significantly less using the bag technique. There was no theatre blood contamination using this method, but significant contamination occurred using the rack. Circulating theatre personnel were minimally contaminated in two cases using the bag method but were grossly contaminated in all ten cases using the rack method. The bag technique is therefore safe and time efficient.

The swab count is an essential part of operating theatre procedure for patient safety and to provide medical staff with an indication of operative blood loss. The count has generally been performed using a swab rack; the circulating nurse transports used swabs to the rack where they are hung in rows of five, in full view of the scrub nurse. Periodically the swabs are counted down on to the floor in batches of five by the scrub nurse and the circulating nurse together. At the end of the procedure all the swabs are rechecked. A new 'bag' method has been devised, which involves the scrub nurse keeping all used swabs on a trolley and periodically counting them in batches of five, checked by the floor nurse, into plastic bags. These are sealed and placed in a designated part of the theatre, after weighing if necessary.

Potential advantages of this technique include a reduced risk of blood spillage and possible contamination of the operating theatre and its personnel; with the swabs already bagged, tidying the operating theatre between cases should also be easier.

A randomized controlled trial to compare the two techniques was undertaken.

Materials and methods

Twenty consecutive operations performed in a single operating suite (two theatres) were randomly allocated to be performed using the swab rack or bag method as described by Plowes¹. The suite was dedicated to ear, nose and throat surgery but a large number of major head and neck procedures were also performed. For each procedure any activities relating to the management of swabs were recorded, timed and analysed using a formal flow process method². This involved reducing all procedures to their simplest parts and constructing a table of these. Each part was timed: the time for the composite parts when added together gave the total time involved in each procedure or activity. The timing and recording were carried out by two nurse investigators (M.H., E.P.B.).

Swab-related activities were classified into three main areas: collection and transport of used swabs during the procedure, including swab counts during the operation; the final swab check and swab disposal; and the time taken to clean the theatre between cases.

The theatres were tiled with 30 × 30 cm tiles and contamination was assessed by counting the number of squares around the swab rack or designated bag area marked with blood. At the end of the procedure the circulating nurse was examined for spots of blood on the clothing or exposed parts of the body and any found were recorded. Assessment of estimates of operative blood loss were made and any problems with the swab counts recorded.

The study could not be performed blind, but the number of theatre

personnel aware of its design and objectives was limited to the three authors.

Results were analysed using Student's *t* test and Fisher's exact test; 95 per cent confidence intervals are given where appropriate³.

Results

A total of 20 operations were analysed: ten in each group with six major, six intermediate and eight minor cases divided equally between the two arms of the study.

In all three areas of swab-related activity the bag technique took significantly less time (Table 1).

There was no contamination of the theatre using the bag technique, compared with a mean of 9.7 (95 per cent confidence interval 6.1-14.1) squares per case contaminated with blood using the rack technique (*t* = 5.7, 18 d.f., *P* < 0.001). In only two cases with the bag technique was the circulating nurse contaminated with blood and this only on the hands and wrists. In all ten cases using the rack system the circulating nurse was contaminated with blood on the wrists and hands, and in nine cases there was contamination of shoes and clothing (Table 2).

Table 1 Times taken for swab-related activities

	Mean time (s)	
	Bag method	Rack method
Collection and transport (5 swabs)	63 (60.1-65.9)	155 (125.8-184.2)*
Final check and disposal	50 (46.1-53.9)	88 (74.1-101.9)†
Cleaning of theatre	277 (248-296)	480 (442-518)‡

Values in parentheses are 95 per cent confidence intervals. **t* = 6.1, *P* < 0.001; †*t* = 5.1, *P* < 0.001; ‡*t* = 8.3, *P* < 0.001 (Student's *t* test, 18 d.f.)

Table 2 Contamination of staff with blood

Site	No. of cases	
	Bag method	Rack method
Hand and wrists	2	10*
Other (clothing and shoes)	0	9†

**P* = 0.0007; †*P* = 0.0001 (Fisher's exact test)

Swabs were weighed in both systems and there was no apparent difference in the assessment of operative blood loss. There were no problems with the swab count using either technique.

Discussion

Moves to abandon the swab rack have gathered momentum in recent years and alternatives, including the bag method, have been proposed^{1,4,5}. Most support for the bag method is, however, largely anecdotal, with little formal analysis of its benefits^{1,4}. This study has shown clearly that the bag technique is a useful alternative to the traditional swab rack method. It is safer, with significantly lower theatre and staff contamination. The time involved in all swab-related activities was significantly reduced with the bag technique and consequently staff exposure to blood-soaked items is reduced. With the current prevalence of human immunodeficiency virus and hepatitis B infection this should mean safer working conditions and lower risk, particularly for the circulating nurse. This is a point of theatre procedure not previously covered in relation to risks of infection⁶⁻⁸. Theatre cleaning time was halved with the bag method because of the reduced contamination and the prior bagging of swabs which could easily be lifted into a second bag. (Double bagging is another safety feature of this technique.) A mean time saving of 3.5 min per patient was made. Following this study the bag technique is now standard practice in this hospital.

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Limitations of laser treatment for malignant dysphagia

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Of 86 patients with inoperable malignant dysphagia, 68 (79 per cent) underwent successful palliation by endoscopic laser therapy, of whom 24 remained well palliated until the time of death. In 18 patients laser treatment was unsuccessful and nine of these underwent intubation, eight successfully. After successful laser therapy, dysphagia recurred in 44 patients a mean of 7.8 weeks later. Of these, 31 received palliation until death by dilatation with or without laser therapy, and 13 required intubation. The overall laser-related complication rate was 12 per cent with a mortality rate of 4 per cent. The intubation-related mortality rate was 9 per cent.

For selected patients with malignant dysphagia, surgery offers good palliation with the possibility of a cure, and with an acceptable complication rate¹. However, for many patients surgery is not an option because of tumour spread, concurrent disease, cachexia, or extreme old age. These patients have a short life expectancy regardless of treatment. The ideal palliation must therefore combine efficacy with consistency, a short inpatient stay, minimal requirement for follow-up treatment and few complications. Several options are now available including intubation with a variety of prostheses, both external and intraluminal radiotherapy, and laser photocoagulation². Since 1986 endoscopic laser therapy has been used for most patients referred with malignant dysphagia to this hospital.

Patients and methods

A total of 86 patients of mean age 72.9 (range 40-90) years received laser treatment as primary therapy for malignant dysphagia between July 1986 and February 1991. Most were referred from other hospitals specifically for palliative therapy for the reasons given in Table 1. A small number of patients presenting directly to this unit were referred for surgery if no metastatic or mediastinal spread was evident on computed tomography and if the patient was fit for surgery. Tumour characteristics are summarized in Table 2. Dysphagia was graded on a simple scale: 1, minimal or no difficulty swallowing; 2, difficulty with solids but able to swallow semisolids; 3, difficulty with semisolids but able to swallow liquids; and 4, difficulty with liquids or unable to swallow anything.

All treatment was carried out with light at 1064 nm provided by a neodymium yttrium-aluminium-garnet laser delivering 70-90 W in pulses of 0.5-2 s duration. Sedation was with intravenous pethidine and diazepam (Diazemuls; Dumex, Aylesbury, UK). Treatment consisted of dilatation if necessary followed by laser treatment in a retrograde manner beginning at the distal margin of the tumour and progressing proximally, as previously described³. In most cases treatments were separated by 72 h to allow necrotic tumour to slough. A summary of the initial laser therapy administered is given in Table 3. Patients who failed to improve with laser therapy were considered for intubation with Atkinson tubes.

Patients with squamous carcinoma were referred for radiotherapy after laser treatment. Fifteen received external radiotherapy (50 Gy). Intraluminal radiotherapy using a Selectron (Nucletron, Veenendaal, the Netherlands) afterloading caesium machine was administered to two patients using a technique described by Rowland and Pagliero⁴, but under sedation with intravenous midazolam rather than general anaesthesia. A further five patients received both intraluminal (10 Gy at 1 cm from the source) and external (50 Gy) radiotherapy. Six patients with adenocarcinoma were also given Selectron treatment (15 Gy).

No routine endoscopic follow-up was arranged in most cases: patients were encouraged to contact the unit directly if their symptoms recurred.

Results

The immediate effects of laser therapy on dysphagia are shown in Figure 1. After treatment, 58 patients could manage a normal

Table 1 Indications for palliative therapy

	No. of patients
Metastases	25
Inoperable tumour at laparotomy	5
Cardiorespiratory disease	24
Cerebrovascular disease	4
Other malignancy	4
Cachexia	13
Old age (mean age 80 years)	11

Table 2 Characteristics of the tumours

	Adenocarcinoma	Squamous cell carcinoma
Location of upper margin of tumour (n)		
Between 20 and 30 cm	7	15
Below 30 cm but without involvement of the cardia	12	21
Below 30 cm with involvement of the cardia	31	0
Length (n)		
≤ 5 cm	22	19
6-10 cm	21	13
> 10 cm	7	4
Mean(s.d.) length (cm)	6.4(2.4)	5.9(2.0)

Table 3 Initial laser treatment

Mean no. of endoscopies	3.2 (1-8)
Mean no. of laser sessions	2.6 (1-6)
Mean laser energy delivered (J)	18 626 (2600-69 254)
Median nights in hospital	8 (0-49)

Values in parentheses are ranges

diet, while ten could take semisolids and some solids. Thus 79 per cent of patients received successful palliation.

In 18 patients laser treatment was unsuccessful. Four patients with very advanced disease attained no improvement following one or two sessions, and no further intervention was felt to be appropriate. In one patient with a very large tumour five treatment sessions were ineffective and palliation was achieved by intubation. In two patients dysphagia persisted owing to abnormal angulation at the cardia: intubation was successful in one but resulted in a fatal perforation in the other. Intubation during the initial treatment was required in six other patients: two for oesophagobronchial fistulation that occurred

after laser treatments, another following a perforation of the oesophagus, and three whose dysphagia persisted despite clearance of intraluminal tumour. Only one of these patients had clear evidence of external compression but all improved following intubation. Five further patients died within 4 weeks of their initial therapy, two following perforation of the oesophagus and one each from aspiration pneumonia, cerebrovascular accident, and myocardial infarction.

Four additional perforations occurred but these consisted of pneumoperitoneum with minimal constitutional upset and prompt recovery, as described by Brooks *et al.*⁵. All laser-related perforations occurred when dilatation and laser treatment were combined in the same session, but it is not clear exactly when the complication occurred.

Follow-up

Of the 68 patients receiving successful palliation by laser, 44 (65 per cent) had recurrence of their symptoms requiring a mean of 4.5 further treatments, at a mean (s.e.m.) interval of 7.8(1) weeks. Nine patients required laser treatment only for regrowth of tumour. In eight a stricture developed without intraluminal tumour and after repeated dilatation six of these

patients underwent intubation with Atkinson tubes. In 27 patients a stricture developed with both tumour and fibrosis, which required both dilatation and laser treatment. Seven of these patients eventually required intubation. The initial and follow-up treatment administered to the 86 patients originally treated by laser is shown in Figure 2.

Of the 86 patients originally referred for laser therapy, 22 required intubation, nine during initial therapy and 13 during follow-up. Intubation resulted in two fatal perforations, and tube dysfunction occurred on eight occasions in seven patients: tumour overgrowth occurred in four, tube displacement in two, and blockage by food in two. The overall intubation complication rate was 45 per cent.

During follow-up two further fatal oesophageal perforations occurred; one was related to intubation, the other to dilatation. In addition, fatal haemorrhage occurred during laser treatment for a tumour that had penetrated the left atrium. Complications of laser-related treatment occurred in 12 per cent of patients. The mortality rate was 4 per cent.

Radiotherapy

The influence of radiotherapy is illustrated in Table 4. Comparison is made between successfully treated patients who received radiotherapy and those who received no radiotherapy. It should be noted that 22 of the 28 patients who received radiotherapy had squamous carcinoma, while all but four of the remainder had adenocarcinoma. Furthermore, patients were referred for radiotherapy only if they appeared fit enough

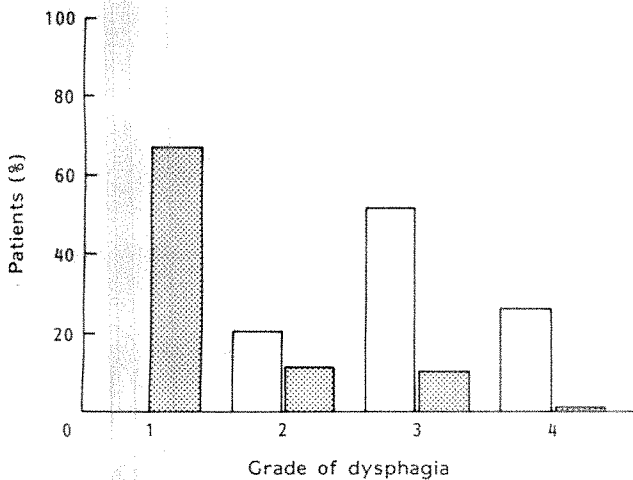


Figure 1 The effect of treatment on dysphagia assessed by grade. 1, minimal or no dysphagia; 2, difficulty with solids; 3, difficulty with semisolids; and 4, difficulty with liquids or complete dysphagia. □, Before treatment; ▨, after treatment

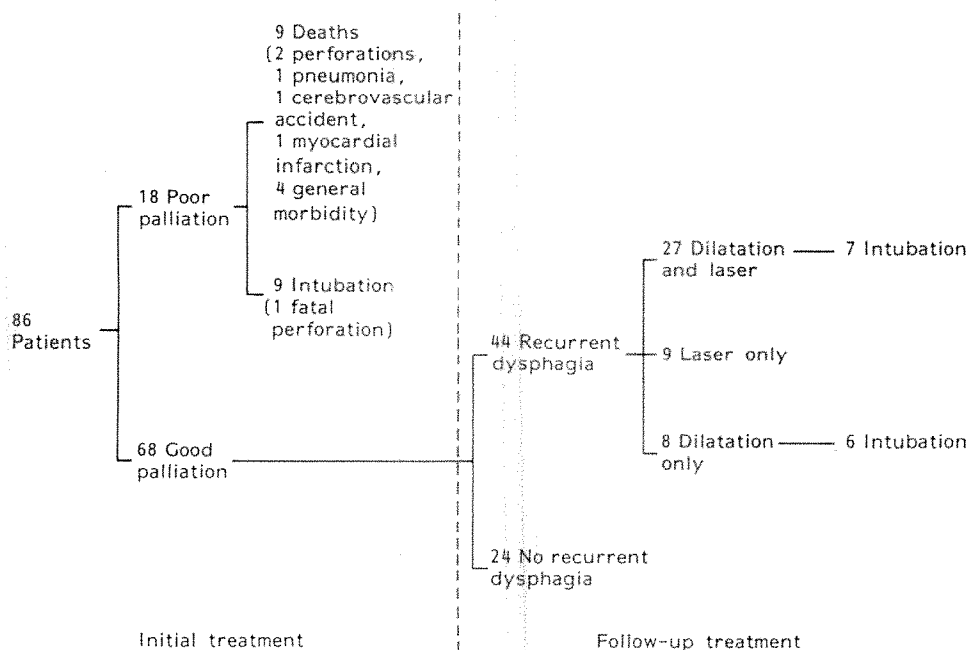


Figure 2 Outcome of 86 patients with malignant dysphagia referred for laser therapy

Table 4 Effect of radiotherapy on recurrent dysphagia, follow-up interval, and survival

	Recurrent dysphagia (n)*	Mean (s.d.) follow-up interval (weeks)	Mean (range) survival (weeks)
No radiotherapy (n = 40)	23 (58)	7.8(6.0)	30 (5-134)
Radiotherapy (n = 28)	19 (68)	7.8(6.1)	34 (6-88)
Intraluminal radiotherapy (n = 13)	12 (92)	12.2(5.6)†	49 (17-88)

*Values in parentheses are percentages; † $P < 0.05$ (intraluminal radiotherapy versus no radiotherapy, Student's *t* test)

...ther treatment and likely to survive long enough. Of the 14 patients with squamous carcinoma who had no radiotherapy, seven were too frail for further treatment, two refused radiotherapy, and one died before treatment was instituted.

In the subgroup of 13 patients who received intraluminal treatment with the Selectron, strictures recurred in 12. In nine of these, recurrent tumour necessitated further laser therapy. Three of these patients required intubation for fibrotic strictures. Nevertheless the patients who received intraluminal radiotherapy required follow-up treatment at significantly longer intervals than those receiving no radiotherapy (mean 12.2 versus 7.8 weeks, $P < 0.05$).

Survival

Five patients are still alive at a mean (s.e.m.) of 56.6 (7.1) weeks after referral. In all, 81 patients have died at a mean (s.e.m.) of 30.9 (3.1) weeks after diagnosis, or 28.1 (2.8) weeks after referral.

Discussion

The success rate in this series of 79 per cent using endoscopic laser therapy for the palliation of malignant dysphagia is comparable to that reported in other series. The complication rate of 12 per cent in the present study is worse than the 4.1 per cent reported in an international enquiry⁶, but is similar to or better than the complication rates reported in some centres⁷⁻⁹. It is now clear that laser therapy fails in a significant proportion of patients, and some develop recurrent dysphagia after initial successful palliation. In this series a total of 22 patients (26 per cent) underwent intubation, because of either initial treatment failure or recurrent dysphagia caused by external compression or fibrosis. It is possible that some would have been better treated by intubation as the primary therapy. The aim of treatment should be to produce the best possible palliation with minimal disruption to the patient's remaining months of life.

Intubation achieves reasonable palliation in most patients. It is quick, cheap, easily performed and widely available¹⁰. The complication rate of intubation, however, is higher than that of laser therapy and the mortality rate¹¹ may be as high as 16 per cent. Furthermore, tube dysfunction occurs in some 40 per cent of patients and there is therefore a requirement for follow-up therapy. The principal limitations of insertion of an endoprosthesis are the high complication rate, and the fact that only a small minority of patients are able to return to an entirely normal diet with the majority being limited to semisolids. It is therefore not surprising that Barr *et al.*¹² found that the insertion of an endoprosthesis after laser therapy increased the likelihood of complications and did not improve relief of dysphagia. The differences between laser therapy and intubation are illustrated by Loizou *et al.*¹³ in a prospective study comparing results from two specialist centres each using one of the two techniques as primary therapy. Significantly more patients received successful palliation by intubation (100 versus 77 per cent) but at the cost of more perforations (13 versus 2 per cent). Furthermore, only 11 per cent of the patients undergoing intubation could manage a normal diet as opposed to 33 per cent in the laser-treated group. In that study laser treatment failures were associated predominantly with cardio-oesophageal tumours.

Intraluminal radiotherapy can provide relief of dysphagia in some 70 per cent of patients with squamous cell carcinoma and in a smaller proportion of those with adenocarcinoma⁴. Similar results are found in combination with external beam radiotherapy¹⁴. These latter treatments may be employed on an outpatient basis¹⁵ but are probably inappropriate as the sole treatment of complete oesophageal occlusion. In a trial by Bader *et al.*¹⁵, intraluminal radiotherapy with iridium-192 after oesophageal recanalization by laser permanently relieved dysphagia in 77 per cent of patients, although six treatment applications at 1-2-week intervals were required. It is possible that a combination of laser and intraluminal radiotherapy will diminish the need for further treatment after initial successful

laser therapy, although in our limited experience most patients who received both treatments eventually developed fibrotic strictures.

The rather high complication rate seen in laser-treated patients in the present study may be a consequence of aggressive treatment to palliate dysphagia as rapidly as possible, with as few treatment sessions as possible. In addition, the procedure is highly operator dependent, probably more so than prosthesis insertion, and a number of operators were learning the technique during the course of the study.

The palliative treatment of inoperable oesophageal malignancy remains far from ideal. When successful, laser therapy may give high-quality palliation with complete relief of dysphagia. We regard endoscopic laser therapy as the treatment of choice for short exophytic tumours. When the malignancy is long, requiring multiple laser treatments to recanalize, considerable fibrosis can result, and it may be preferable to palliate by insertion of an endoprosthesis in a single session. Intubation should also be used for those patients with a fistula or external compression. Laser therapy is useful in tumours involving the upper part of the oesophagus where it might not otherwise be possible to site a tube, and it is also useful in clearing tubes overgrown by tumour. The two treatments should be seen as complementary rather than competing.

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Case report

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Total dysphagia from intramural haematoma following sclerotherapy for oesophageal varices

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Oesophageal intramural haematoma is rare, but it has been reported after emesis, Mallory-Weiss tears and in association with trauma. It also occurs spontaneously. Presenting symptoms are dysphagia, odynophagia, haematemesis and chest pain. A patient is reported with intramural haematoma following elective injection sclerotherapy and presenting with acute dysphagia.

Case report

A 59-year-old man was admitted for elective injection sclerotherapy for oesophageal varices secondary to alcoholic hepatic cirrhosis. He had presented initially 5 months earlier with severe haematemesis, when varices were identified and injected. The patient had undergone four further sessions of sclerotherapy over a 2-month period with an uneventful outcome. On his fifth presentation, varices were injected with 15 ml ethanolamine oleate through a rigid oesophagoscope.

Over the following 18 h the patient complained of progressive chest tightness and dysphagia. Results of clinical examination were normal and vital signs remained stable. Electrocardiography and chest radiography showed no abnormality but a Gastrografin (Schering Health Care, Burgess Hill, UK) swallow demonstrated compression of the entire wall of the oesophagus resulting in proximal hold-up. Computed tomography revealed an intramural soft tissue mass extending from the aortic arch to the diaphragm and compressing the lumen (Figure 1). The soft tissue was of the same density as the aorta, confirming the clinical impression of an intramural haematoma. The patient was managed conservatively and his symptoms settled within 72 h. At follow-up endoscopy 3 months later there was no evidence of stenosis and no further complications occurred at subsequent sclerotherapy.

Discussion

Sclerotherapy has become the treatment of choice for oesophageal varices, but there is no consensus as to whether the sclerosant should be injected into the varices or the perivascular tissues; both approaches appear to be equally effective¹. While some intraluminal bleeding is inevitable, it is rarely serious.

Intramural haematoma is, however, rare. Anticoagulant therapy, impaired coagulation and thrombocytopenia complicating leukaemia and aplastic anaemia have all been described as contributing factors. Desmorat *et al.*² reported three cases, an incidence of 1.6 per cent, but Kahn *et al.*³ reported only

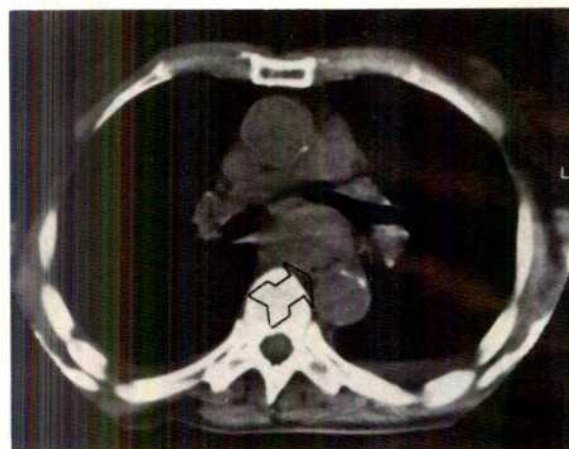


Figure 1 Computed tomographic scan of thorax showing oesophageal lumen (open arrow) compressed and partially occluded by an intramural haematoma

one case in 304 patients receiving a total of 1336 injections. There have been few other reports of intramural haematoma complicating injection sclerotherapy.

Post-mortem studies have demonstrated that tissue necrosis associated with injection of sclerosant can extend deep into the submucosa and muscularis. It has been suggested that raised portasystemic pressure and haemostatic defects, in addition to submucosal necrosis, can result in dissection⁴.

Symptoms of severe complete dysphagia may suggest the diagnosis. The possibility of haematoma may also be raised by retrosternal pain, although this is more frequently the result of tissue necrosis.

Management should be conservative as symptoms usually begin to resolve spontaneously over 36–72 h and disappear completely in 2–3 weeks. Skillington *et al.*⁵ reported an iatrogenic perforation during endoscopic examination of an intramural haematoma, which necessitated oesophagectomy.

Further injection sclerotherapy is not contraindicated: it has been suggested that the submucosal healing along the dissection plane may aid in the obliteration of residual varices.

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Mechanism of action of injection therapy for bleeding peptic ulcer

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The effects of intramucosal injection of 1:100 000 adrenaline, 5 per cent ethanolamine and normal saline were determined in experimentally created, acutely bleeding gastric mucosal wounds in rabbits. The mean (s.d.) bleeding rate was decreased from 2.3(0.4) to 0.2(0.02) ml/min by adrenaline ($P < 0.01$), but increased by 1 ml 5 per cent ethanolamine to 4.0(0.6) ml/min ($P < 0.05$). Normal saline had no haemostatic effect, suggesting that local tamponade is not important. In separate experiments endoscopic injections of 5 per cent ethanolamine, 1:100 000 adrenaline and normal saline were made in the gastric antrum of rabbits. After 48 h the degree of inflammation was greatest with ethanolamine but, despite tissue necrosis and venous thrombosis, neither endarteritis nor arterial thrombosis occurred. Injections of 5 per cent ethanolamine and 80 per cent ethanol placed next to the ear arteries of rabbits caused local ulceration and necrosis, but endarteritis and arterial thrombosis were again absent.

The prognosis of patients presenting with bleeding peptic ulcer is improved by endoscopic injection therapy but the optimum regimen is unclear.

Chung *et al.*¹ showed that active bleeding can be stopped by injection of dilute adrenaline. However, relatively large fluid volumes were used (6–10 ml, 1:10 000) and it is possible that the haemostatic effect was caused by local tamponade rather than pharmacological action. Rebleeding could occur as tissue oedema and vasoconstriction resolve. Other investigators have injected a range of sclerosing agents around or into the bleeding ulcer^{2–4}; these induced an inflammatory response leading to thrombosis but the effect was not immediate and sclerosants may therefore not be useful in acute bleeding. Injection of sclerosants could even be harmful; it is known, for example, that their use as therapy for oesophageal varices is associated with a significant risk of ulceration⁵ and a similar effect in the gastric mucosa could enlarge a peptic ulcer, predisposing to perforation and impaired healing. Nevertheless, injection of both adrenaline and sclerosants has been used in several studies of bleeding peptic ulcer^{6–8}, and one of these suggested that a combination was better than adrenaline alone⁶.

The experiments described in this study were designed to determine whether haemostasis can be effected by local tamponade, whether adrenaline causes endarteritis and arterial thrombosis and whether injection of a sclerosant stops acute ulcer bleeding and causes endarteritis. To answer these questions by examining injected ulcers is difficult because of the confounding effects of inflammation from the ulcer, particularly since the inflammation itself may be associated with endarteritis. The haemostatic effects of a range of injection materials were therefore examined in an experimental model of acute bleeding in which gastric mucosal wounds were created, and the histological effect of injections in the rabbit stomach and ear arteries studied.

Materials and methods

Acute mucosal wounds

Acute bleeding gastric wounds were created in rabbits treated with heparin.

Six New Zealand White rabbits (weight 3.5–5.5 kg) were fasted for 12 h and anaesthetized using a combination of intravenous midazolam, Hypnorm (Janssen Pharmaceuticals, Wantage, UK) and a halothane–oxygen mixture. The stomach was exposed through a midline abdominal incision and a gastrotomy made. Heparin, 250 units per kg body-weight, was injected into an ear vein. A total of six to eight wounds were made in the body and gastric antrum of each rabbit using

a scalpel. Discs of tissue 2.5–3.8 mm in diameter were excised; histological examination revealed mucosa alone in all cases. Bleeding from each wound was measured by adsorption of blood on to preweighed triangular segments of blotting paper which were reweighed after 30–60 s, depending on the rate of bleeding. Only wounds bleeding at a rate of > 1 ml/min ('basal blood loss') were studied.

Single injections of 1 ml normal saline, 1 ml 1:100 000 adrenaline or 1 ml 5 per cent ethanolamine were placed beneath the bleeding wound using 23-Fr needles (outside diameter 0.6 mm). Injections were given in random order. Blood loss was measured for the 60-s period immediately after the injection and in some cases 5 min later. At the end of the experiment the animals were killed by an overdose of barbiturate, the stomach was removed, fixed in formalin and stained with haematoxylin and eosin. The wounds were examined by a pathologist (A.L.) who was unaware of the injected materials. A subjective assessment of the histological changes was made.

Histological effects of injection

The histological effects of injected materials on the rabbit gastric mucosa were examined in three further New Zealand White rabbits, weight 3.5–5.5 kg. After a 12-h fast each animal was sedated by a titrated injection of midazolam into an ear vein. Oesophagogastroscopy was performed using an Olympus P10 paediatric forward-viewing gastroscope (Olympus, Keymed, Southend-on-Sea, UK). Despite the prolonged fast and prevention of coprophagy the stomachs invariably contained a large amount of partially digested food, although antral visualization was possible and the procedure was well tolerated.

In each rabbit single injections of each of 1 ml 1:100 000 adrenaline, 1 ml normal saline and 1 ml 5 per cent ethanolamine were made using a variceal sclerotherapy needle (Keymed) at separate sites in the gastric antrum. The injection sites were carefully mapped and marked with methylene blue. No complications were associated with the injections. The animals were killed 48 h later and the stomachs fixed in formalin and examined histologically.

To examine further the arterial effects of injected sclerosants 1-ml injections of 5 per cent ethanolamine were placed next to the ear arteries of two rabbits (four injections) and 1-ml injections of 80 per cent ethanol positioned next to these vessels in a further two animals (four injections). The animals were killed 24 (two rabbits) or 48 h (two rabbits) later and the ear sections examined histologically.

Ethical considerations

These experiments were performed after obtaining a project licence from the Home Office.

Statistics

Student's paired *t* test was used to determine differences between means.

Results

Acutely bleeding gastric wounds

The mean (s.d.) blood loss before injection around the wounds was 2.3(0.4) ml/min ($n = 27$). In six of these animals bleeding rates were measured again after 5 min; blood loss was very similar at 2.0(0.8) ml/min.

Table 1 shows the effect of injection of saline, adrenaline and ethanolamine on blood loss. Normal saline did not significantly affect the rate of loss, but bleeding was significantly reduced 1 and 5 min after injection of adrenaline ($P < 0.01$). Ethanolamine significantly increased the initial bleeding rate ($P < 0.05$), although blood loss returned to basal values after 5 min.

Histological examination of excised gastric mucosa showed remarkable uniformity in the depth of the wounds, the submucosa being intact in all cases. Mucosa surrounding wounds was oedematous but not significantly inflamed.

Histological effects of injections

Gross examination of stomachs removed 48 h after endoscopically administered injections revealed a range of findings. The injection sites after treatment with ethanolamine were more oedematous and ulcerated than those associated with adrenaline; the sites of saline injection were not grossly abnormal. Histologically the areas injected by adrenaline and normal saline showed oedema, relatively mild inflammation, or localized necrosis at the injection site. There were no vascular changes. Sites of ethanolamine injection showed a similar degree of mucosal inflammation, but inflammation in the submucosa was much more severe and there was focal involvement of the muscularis propria. Venous thromboses were seen but neither endarteritis nor arterial thrombosis was observed despite careful examination of multiple levels (Figure 1).

Table 1 Blood loss associated with acute mucosal wounds

	Blood loss (ml/min)	
	1 min	5 min
Basal ($n = 27$)	2.3(0.4)	2.0(0.8)
Adrenaline ($n = 9$)	0.2(0.02)*	0.35(0.02)*
Saline ($n = 9$)	1.7(0.3)	1.8(0.4)
Ethanolamine ($n = 9$)	4.0(0.6)†	2.1(0.3)

Values are mean (s.d.). Twenty-seven wounds were observed for 1 min, and six of these for 5 min. All wounds were then injected. * $P < 0.01$; † $P < 0.05$ (both versus basal values, paired t test)



Figure 1 Photomicrograph of rabbit gastric mucosal section at the site of ethanolamine injection. Oedema, mucosal necrosis and marked polymorphonuclear infiltration are present. The arteries are histologically normal, but the vein shows fibrous intimal proliferation and thrombosis. (Haematoxylin and eosin stain, original magnification $\times 160$)

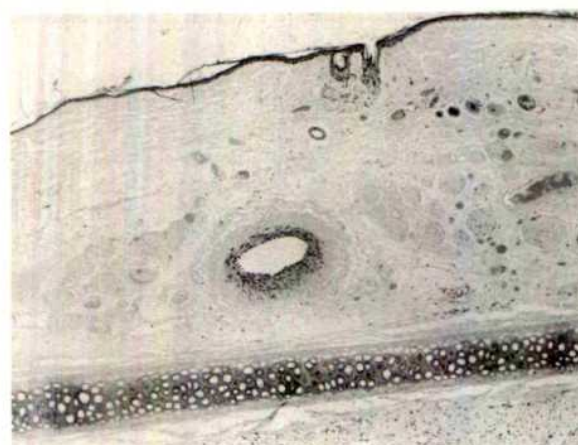


Figure 2 Photomicrograph of rabbit ear section 48 h after ethanolamine injection. Extensive necrosis has occurred from epidermis to cartilage. An artery is present within the necrotic area, which demonstrates mild adventitial inflammation, but there is no endothelial abnormality and no evidence of thrombosis. (Haematoxylin and eosin stain, original magnification $\times 64$)

Examination of the ears showed extreme necrosis from the surface epidermis to the underlying cartilage, with a marked polymorphonuclear infiltrate at the edges of the necrotic areas. Arteries were found at the centre of the necrosis. After 24 and 48 h the endothelium was consistently normal following both ethanol and ethanolamine injection. The arterial lumen was invariably patent with no evidence of arterial thrombosis. In some sections there was mild polymorphonuclear infiltration in the adventitia. In contrast, venous inflammation and thrombosis were commonly seen (Figure 2).

Discussion

The rabbit stomach was chosen for study because in preliminary experiments endoscopy was found to be easy and ulcers could be created by injection of sclerosants. The rabbit has similar gastric anatomy and physiology to the human and has previously been used as an experimental model of bleeding ulcers⁹.

The model of mucosal bleeding used in these experiments differs in many respects from the clinical problem of bleeding peptic ulcer in which an often atherosclerotic artery is eroded. The model has evaluated the efficacy of injection therapy in mucosal rather than arterial bleeding. Furthermore, peptic ulcers are commonly associated with a vigorous fibrous reaction with endarteritis whereas the arteries examined histologically were essentially normal, healthy vessels. Despite these limitations the present findings suggest that the haemostatic effect of adrenaline is caused by vasoconstriction rather than local tamponade because injections of similar volumes of normal saline had no effect on the rate of bleeding. It could be argued that the fibrotic reaction around a chronic ulcer may result in higher pressure, and hence a tamponade effect, following injection of saline and it is therefore possible that this conclusion does not apply to bleeding peptic ulcers in humans. We believe this argument to be flawed for three reasons. First, considerable swelling was caused in the present experiments by injection of saline suggesting considerable intramucosal tension. Second, if mucosal bleeding was not suppressed by saline injection it seems most unlikely that arterial haemorrhage, which is of considerably higher pressure, would be decreased. Third, injections of adrenaline administered at some distance from the bleeding area were haemostatic.

In the present experiments ethanolamine increased active bleeding although rates returned to basal levels within 5 min. This suggests that injection sclerotherapy with ethanolamine, without simultaneous injection of a vasoconstricting agent, is

not effective treatment for active haemorrhage and may actually exacerbate bleeding.

As expected, the histological studies showed that the extent and severity of mucosal inflammation were greater after the injection of a sclerosant than after that of adrenaline or saline. No attempt was made to quantify the degree of inflammation or necrosis since there were clear and obvious differences between the groups of animals as shown in *Figures 1* and *2*. An unexpected finding was that despite this vigorous reaction, leading to tissue necrosis and venous thrombosis, neither endarteritis nor arterial thrombosis occurred. This was confirmed in the ear experiments in which injections accurately positioned adjacent to the arteries were possible.

In conclusion, this study suggests that saline injection into bleeding gastric mucosa has little influence on blood loss and no important histological effect. Injection of dilute adrenaline markedly reduced mucosal blood loss with little tissue damage and did not lead to endarteritis. While sclerosants (5 per cent ethanolamine and 80 per cent ethanol) caused tissue necrosis and venous thrombosis, no evidence that they caused endarteritis was found, nor did their injection reduce mucosal blood loss. These findings may be relevant to the choice of materials used in clinical practice for endoscopic injection therapy of bleeding ulcers.

Acknowledgements

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Laparoscopic repair of perforated peptic ulcer

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Perforated duodenal ulcer is often repaired by suture over an omental patch, a procedure that normally requires laparotomy. Mouret and colleagues¹ described laparoscopic investigation of perforated peptic ulcer and in three patients reported sealing the perforation with an omental patch held in position by fibrin glue. This paper reports the development of a laparoscopic technique for sutured patch repair of perforated peptic ulcer.

Surgical technique

After diagnosis of perforated peptic ulcer a nasogastric tube and a urinary catheter (Vygon, Cirencester, UK) are inserted. Antibiotics and intravenous H₂-receptor antagonists are administered with the premedication. In the operating theatre the patient is prepared as for an open procedure. Through an umbilical stab incision pneumoperitoneum is established with a Veress needle followed by introduction of the laparoscope through an 11-mm cannula. Laparoscopy is performed in the reversed Trendelenburg position. Another 11-mm cannula is established under laparoscopic control in the midline at the epigastrium just distal to the xiphisternum. Two further 5-mm cannulae are inserted in the right hypochondrium, in the mid-clavicular and anterior axillary lines.

After irrigation with warm saline the perforation is identified and the laparoscope then moved to the upper 11-mm cannula to obtain a more direct view of the perforation. The operator can then use the lower 11-mm and lateral 5-mm cannulae for suturing or retraction, leaving the remaining 5-mm cannula for insertion of sutures. An Endosuture (Endoknot; Ethicon, Wordersstedt, Germany) is loaded into a 5-mm reducing sheath and introduced, needle first, into the peritoneal cavity through the medial 5-mm cannula. A needle holder (5 mm; Karl Storz, Culver City, California, USA) introduced through the 11-mm cannula is used to grasp the needle. With the assistance of a grasping forceps held in the left hand the needle is passed through normal duodenum a small distance removed from the edge of the perforation. This allows the needle to pass easily with no risk of tearing the ulcer edge and extending the perforation. A patch of omentum is mobilized and brought up over the perforation with the left hand. A further pass with the needle through the omentum approximates the patch to the ulcer (Figure 1). A 3-mm needle holder is then passed down the suture-bearing cannula and the needle withdrawn. An extracorporeal Roeder knot² is tied in the suture and pushed down to fix the patch over the perforation. Additional sutures can be passed as required to surround the perforation. It is sometimes necessary to pull the duodenum down to expose the ulcer where there is an overhanging liver edge. Alternatively, elevation of the liver edge may be required. In this situation a fifth cannula at the level of the umbilicus in the right mid-clavicular line may be useful to allow the assistant to maintain retraction.

When the perforation has been closed, peritoneal lavage is performed with 2–3 litres warm saline for 15–30 min to ensure complete removal of contaminants. Special attention is paid to the suprahepatic and subhepatic spaces, the left subdiaphragmatic space and the pelvic

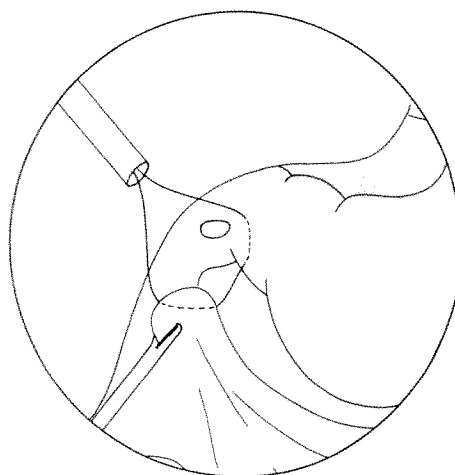


Figure 1 A suture is passed through the duodenal wall and a piece of omentum

cavity. The bowel loops are agitated in saline using the irrigation instrument or by gently shaking the patient. After lavage the fluid is aspirated and the cannulae withdrawn. Wounds are closed with polydioxanone (PDS; Ethicon) where required and with Steri-strips (Ethicon).

Results

This technique has been used in six patients: four men and two women aged from 36 to 61 (mean 45) years. The perforation developed a mean of 9.3 h before the operation.

At laparoscopy all patients were found to have perforated duodenal ulcers. The operation took a mean time of 108 (range 85–160) min. The mean number of opiate injections after surgery was 3.7 (range 1–7). Water-soluble contrast meals were given to all patients 3 days after operation. No leakage was demonstrated and no postoperative complications occurred. The mean hospital stay was 6.5 (range 5–10) days.

Discussion

The laparoscopic patch repair described offers an alternative to open surgery and avoids the dangers of conservative management. The technique allows an omental patch to be securely sutured under laparoscopic vision. The surgeon can therefore perform the same operation as normal, including lavage of the contaminated peritoneal cavity, but without a large abdominal incision. This may lead to reduced wound pain and shorter convalescence. The operation currently takes 108 min, slightly longer than open patch repair. With increasing experience and practice with laparoscopic suturing techniques this time will decrease. The operation can be performed easily by surgeons familiar with laparoscopic cholecystectomy and may become the method of choice for the treatment of perforated peptic ulcer.

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Selective necrosis in hamster pancreatic tumours using photodynamic therapy with phthalocyanine photosensitization

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Photodynamic therapy (PDT) is often thought to be able to effect selective tumour necrosis. This therapeutic selectivity, based on transient differences in tumour: normal tissue photosensitizer concentration ratios, is rarely useful clinically in extracranial tumours, although PDT itself may be of value by virtue of the nature of the damage produced and healing of normal tissue by regeneration. This report describes the effects of PDT on normal pancreas and chemically induced pancreatic cancers in the hamster, where a different mechanism of selective necrosis may be seen. Photosensitizer distribution in normal and neoplastic pancreas was studied by chemical extraction and fluorescence microscopy. Correlation of distribution studies with necrosis produced by PDT shows that the photodynamic dose (product of tissue concentration of sensitizer and light dose) threshold for damage is seven times as high for normal pancreas as for pancreatic cancer. Tumour necrosis extended to the point where tumour was invading normal areas without damaging the normal tissue. In rat colonic cancer, photodynamic dose thresholds in tumour and normal tissue are similar and so such marked selectivity of necrosis is not possible. The reason for this selectivity in the pancreas is not clear, but recent evidence has suggested a difference in response to PDT between normal and neoplastic pancreatic cell lines and the presence of a singlet oxygen scavenger in normal pancreas is postulated. Furthermore, the present fluorescence microscopy studies suggest that tumour stroma contains the highest level of photosensitizer and thus receives the highest photodynamic dose during PDT. These results suggest a possible role for PDT in treating small pancreatic tumours or as an adjuvant to other techniques, such as surgery, that reduce the main bulk of tumours localized to the pancreas.

Photodynamic therapy (PDT) has attracted much interest over the past 10 years as the concept of selective retention of photosensitizers in malignant tumours has raised the possibility of their selective destruction. In general, this dream has not been realized. For all solid extracranial tumours so far studied, the ratio of sensitizer concentration between tumour and normal tissue does not exceed 3:1. Few quantitative studies of necrosis have been reported but, in most that have been carried out and well documented, there is just as much damage to normal tissue as to malignant areas when both are exposed to the same light dose. Clinically, this may be acceptable if damage to normal areas heals mainly by regeneration of normal tissue. However, there are circumstances under which truly selective necrosis can be achieved. The most notable is in the brain, where the photosensitizer ratio between tumour and normal tissue can be as high as 28:1; necrosis of transplanted gliomas has been shown in mice and rats without damage to adjacent normal brain tissue^{1,2}.

Truly selective necrosis has been shown in chemically induced colonic cancers in rats, based on transient differences in pharmacokinetics of the photosensitizer. However, under the circumstances in which this could be achieved, it was possible to obtain only 2 mm of necrosis in the tumour and this did not

include the region where the cancer invaded adjacent normal tissue³.

Two thresholds must be exceeded for a PDT effect to be seen. The first is the absolute concentration of sensitizer in the tissue. If this is not reached, the sensitizer is inactivated by photobleaching, presumably before enough singlet oxygen is formed to produce a biological effect⁴. The second is the product of the absolute concentration of the sensitizer and the light dose at each point in the target tissue. If the concentration is just below the first threshold in normal areas but just above in the tumour, selective damage is possible, as was shown in the colon experiments³. However, the sensitizer doses in these studies were well below those normally used. This inevitably resulted in a very small extent of necrosis being produced, although if the target pathology is <2 mm thick this may be acceptable. For example, *in situ* bladder carcinoma may be amenable to treatment using these dosimetry principles⁵.

The situation with the pancreas may be different. Recent reports⁶ have suggested that pancreatic carcinomas induced by 2,2'-dioxodi-*n*-propylnitrosamine (BOP) in Syrian golden hamsters may be more susceptible to PDT than normal pancreatic tissue after sensitization with dihaematoporphyrin ether (DHE). In the present study, the microscopic distribution of aluminium sulphonated phthalocyanine (AlSPc) was examined in normal and neoplastic pancreas using fluorescence microscopy with a charge-coupled device (CCD) camera; these results were correlated with the distributions measured by

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chemical extraction and with the response to light. The light dose was varied to determine the photodynamic threshold for damage to the normal pancreas and pancreatic tumour.

Materials and methods

Experiments were carried out on female Syrian golden hamsters. For studies on normal pancreas, animals aged 6–10 weeks and weighing 100 g were used. Pancreatic tumours were induced by ten subcutaneous injections of 10 mg/kg BOP at 1 week intervals⁷. Animals treated with carcinogen were used between 16 and 24 weeks after the first injection. The photosensitizer used was AISPc. This was obtained from Ciba-Geigy (Basel, Switzerland), and made up in 1 mol/l NaCl to a concentration of 2 mg/ml. Sensitization was by intravenous injection of 5 mg/kg into the inferior vena cava at laparotomy, at which time the presence or absence of tumour was confirmed.

Distribution studies from chemical extractions

Animals injected with 5 mg/kg AISPc were killed 4, 24 or 48 h after sensitization. Pancreatic tissue was removed at autopsy and stored at -4°C before assay. AISPc was extracted using 0.1 mol/l NaOH as previously described⁸. Briefly, the assay required dissolution of a weighed amount of tissue in NaOH by incubation of the mixture in a water bath at 50°C for 4 h. The resulting mixture was spun down and the AISPc content of the supernatant determined using fluorescence measurement by comparison with standard curves prepared using 0.1 mol/l NaOH on unsensitized pancreas or pancreatic tumour to which known amounts of photosensitizer had been added.

Fluorescence microscopy and photometry

Animals sensitized with 5 mg/kg AISPc were killed 48 h after injection. Pancreatic tissue (tumour or normal) was removed at autopsy and immediately frozen using isopentane and liquid nitrogen. Frozen sections (10 μm) were used for fluorescence microscopy as previously described^{9,10}. Using a combination of phase-contrast and light microscopy of haematoxylin and eosin stained sections cut immediately adjacent to those used for fluorescence microscopy, it was possible to identify areas of interest. The technique of fluorescence microscopy has been described recently¹¹, but is summarized here. Frozen tissue sections on glass slides were placed on the stage of an inverted microscope (IMT-2; Olympus, Tokyo, Japan) with epifluorescence and phase-contrast attachments, and an 8-mW helium-neon laser (632.8 nm) used as the excitation source. The laser output was passed through a 10-nm bandpass filter, centred at 633 nm, to remove extraneous light and then directed on to the section using a liquid light guide and dichroic mirror. Fluorescence was detected between 665 and 700 nm, using a combination of bandpass (Omega Optical, Vermont, USA) and longpass (RG665; Schott, Mainz, Germany) filters, and imaged using the cryogenically cooled CCD camera (Model 1; Wright Instruments, London, UK, resolution 400×600 pixels) fitted to the microscope. Image processing and camera operation were carried out using a personal computer. This slow-scan CCD system has sensitivity comparable to that of photomultiplier photon counting detection and is significantly superior to conventional video camera imaging¹². The black-and-white digital fluorescence images were falsely colour-coded by image processing software and photographed for comparison with the corresponding images from adjacent stained sections. Computer software was used to calculate values for mean fluorescence intensity within a rectangle drawn over areas of interest on the monitor¹¹. With tumour-bearing pancreata, values were obtained from tumour epithelium and stroma, together with values for normal acinar tissue and ducts within the same pancreas.

Photodynamic therapy

Normal pancreas and pancreatic tumours (≥ 5 mm) were treated at laparotomy 48 h after sensitization. Red light (675 nm) from a copper vapour pumped-dye laser (Oxford Lasers, Oxford, UK) was delivered using a 200- μm fibre just touching the tissue to be irradiated. Energy doses studied were 50, 100 and 200 J for normal pancreas and 50, 25 and 12.5 J for pancreatic tumour, using a laser power of 25 mW for 50 J or lower or 50 mW for levels above 50 J. Control experiments were carried out on unsensitized animals using 50, 100 or 200 J for normal pancreas and 50 J for pancreatic tumour using the same power levels. Necrosis was assessed at autopsy 72 h after light exposure, both macroscopically and microscopically, using haematoxylin and eosin stained sections of the treated areas.

Results

Distribution studies from chemical extractions

As shown in Figure 1, AISPc concentration was maximal in normal pancreas at 4 h (the shortest time interval studied) and decreased with time after injection. In tumours, peak concentration was noted at 24 h. The tumour:normal tissue ratios at 4, 24 and 48 h were 0.74:1, 3.0:1 and 2.3:1 respectively.

Fluorescence microscopy and photometry

Fluorescence in normal pancreas was greatest in ducts and blood vessel walls (Table 1). The cellular areas of acini were poorly fluorescent although there was slightly more fluorescence at the peripheries of acini (Figure 2).

Pancreata in tumour-bearing animals selected for fluorescence microscopy contained areas of normal pancreas (Figures 3 and 4). Fluorescence was greatest in stromal areas (Table 1). Fluorescence from tumour epithelium was less than from stromal areas, but was slightly greater than from normal acinar tissue.

Photodynamic therapy

Although the maximum tumour:normal tissue ratio of AISPc concentration occurred at 24 h, the standard deviations of these concentrations were smallest at 48 h, so this was the time chosen for PDT. These results are shown in Table 2. There was little difference in macroscopic and microscopic appearances between sensitized (Figure 5) and unsensitized normal pancreas

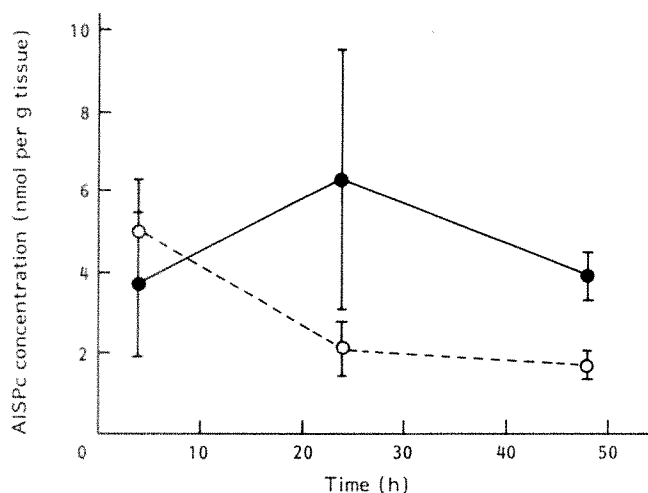


Figure 1 Mean (s.d.) aluminium sulphonated phthalocyanine (AISPc) concentration in (○) normal pancreas and (●) pancreatic tumour versus time from photosensitizer administration ($n \geq 3$ for each value). Although the tumour:normal tissue ratio was highest at 24 h, 48 h was chosen for fluorescence studies and photodynamic therapy as the variation of AISPc concentration was least at this time

Table 1 Fluorescence photometry of normal pancreas and pancreatic tumour 48 h after photosensitizer administration

	Fluorescence intensity (counts/pixel)
Normal tissue	
Acinar areas	53(14.7)
Ducts	96(11.3)
Tumour	
Epithelium	68(6.9)
Stroma	155(30)

Each value is the mean (s.d.) of readings from at least five different specimens. Background fluorescence values using unsensitized pancreatic sections on plane glass slides have been subtracted

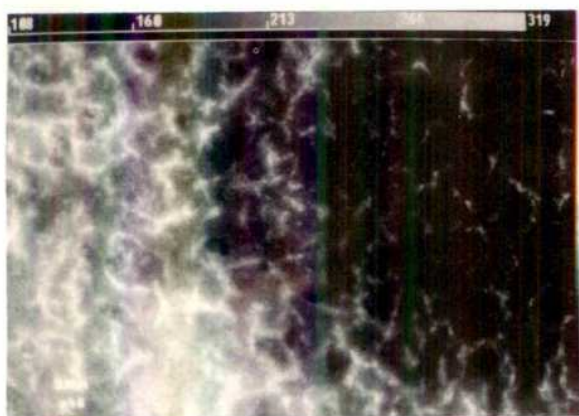


Figure 2 Fluorescence micrograph of normal pancreas 48 h after photosensitizer administration. Fluorescence is localized to cell membranes and at the peripheries of acini. The grey fluorescence intensity scale is at the top of the image. (Actual size 200 × 120 µm)

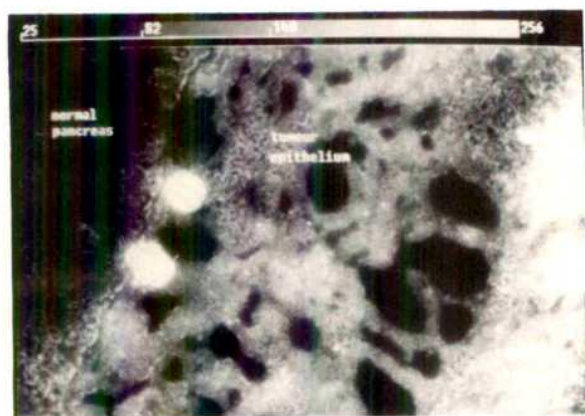


Figure 3 Fluorescence micrograph of frozen section of pancreatic tumour 48 h after photosensitizer administration. Maximum fluorescence is noted in tumour stroma (bottom right). Tumour epithelium fluorescence is higher than that of normal acinar tissue. (Actual size 800 × 550 µm)

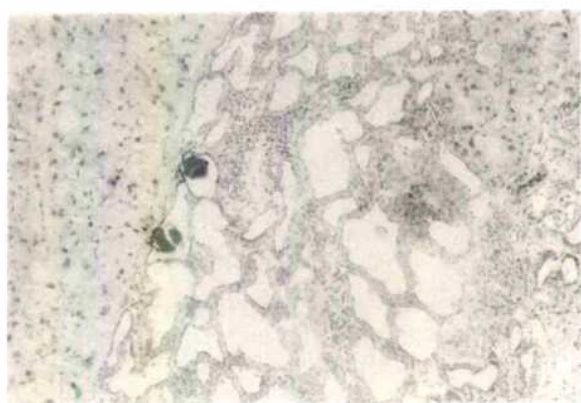


Figure 4 Micrograph of frozen section used in Figure 3 after haematoxylin and eosin staining. This permits visual comparison of the fluorescence image. (Actual size 800 × 550 µm)

treated with up to 100 J, suggesting no PDT damage but slight thermal damage, with oedema and vascular stasis, at the site of irradiation (<2 mm in diameter). With 200 J (Figure 6), there was evidence of haemorrhagic coagulative necrosis on light microscopy in sensitized animals, indicative of photodynamic damage. This was different from thermal controls in which, although necrosis was present, there was no evidence of haemorrhage and the inflammatory cell infiltrate was less marked. Adjacent viable pancreas (Figure 6) exhibited some damage with a moderate inflammatory cell infiltrate, although this had not progressed to coagulative necrosis. With light doses of 50 J and above, three of nine sensitized animals demonstrated

gastric ulcers in areas adjacent to treated pancreas. All sensitized tumours, even those treated with only 12.5 J, demonstrated macroscopic evidence of coagulative haemorrhagic necrosis after PDT, which was confirmed on microscopy (Figure 7), although no damage was evident in adjacent normal pancreas. Tumour necrosis was noted to be <5 mm in diameter with 12.5 J, and a viable rim of surviving tumour in areas furthest from the site of light application was seen. When 25 or 50 J light doses were used, damage appeared to extend to the edges of tumour nodules 5 mm in diameter (*n* = 2), and up to 8 mm in larger tumours. No damage was seen in adjacent normal pancreas (Figure 7) or stomach in any of these tumour-bearing animals at the light doses used (maximum 50 J).

Table 2 Results of photodynamic therapy of hamster pancreas at 48 h after photosensitizer administration

Light dose (J)	Normal	Tumour
12.5	—	Haemorrhagic coagulative necrosis
25	—	Haemorrhagic coagulative necrosis
50	No effect	Haemorrhagic coagulative necrosis
100	No effect	—
200	Damage	—

Necrosis was assessed histologically from tissues taken at necropsy 72 h after light administration. Normal pancreas demonstrated damage only after light doses of 200 J, whereas tumour necrosis was seen after even as little as 12.5 J

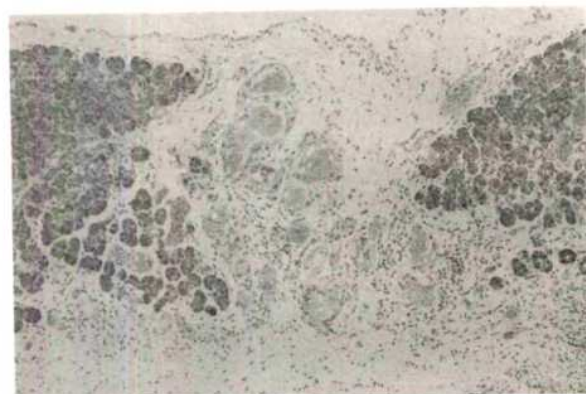


Figure 5 Micrograph of normal pancreas 72 h after photodynamic therapy using a light dose of 100 J. There is oedema and vascular stasis suggestive of thermal damage. (Actual size 800 × 550 µm)



Figure 6 Micrograph of normal pancreas 72 h after photodynamic therapy using a light dose of 200 J. There is a relatively well defined area of haemorrhage and coagulative necrosis suggestive of photodynamic damage (upper left). Adjacent pancreas exhibits some damage with a moderate inflammatory cell infiltrate, but damage has not progressed to coagulative necrosis. (Actual size 800 × 550 µm)

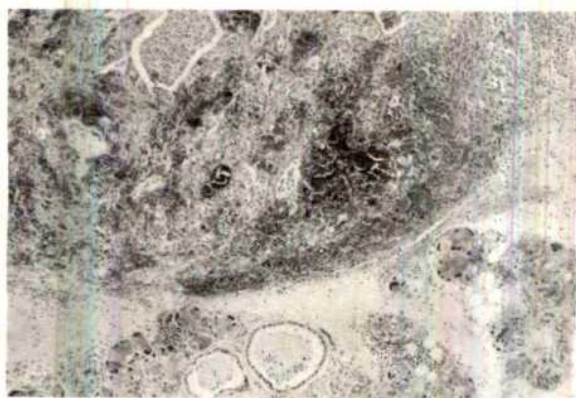


Figure 7 Micrograph of edge of tumour nodule 72 h after photodynamic therapy using a light dose of 25 J. Coagulative necrosis and haemorrhage is seen in the tumour, whereas adjacent normal pancreas (bottom right) is unaffected. (Actual size $800 \times 550 \mu\text{m}$)

On the basis of the above, the minimum light dose required to produce damage to normal pancreas at 48 h was 200 J. The threshold photodynamic dose required to produce damage was thus 200×1.7 (light dose $\times$ mean concentration of AISPc at 48 h), that is 340 arbitrary units. By a similar method, for pancreatic tumour, the threshold dose was approximately 12.5×3.9 , that is 49 arbitrary units. Thus the threshold photodynamic dose for damage to normal pancreas was about seven times as high as for damage to pancreatic tumour.

Discussion

Selective destruction of tumours within their organ of origin without damage to the normal tissue in which the tumour arose is the aim of all local treatment of cancer. The selectivity shown in transplanted brain tumours in mice² and dimethylhydrazine-induced colonic tumours in the rat³ relies on transient differences in photosensitizer concentration, related to preferential retention of photosensitizer in tumour tissue. In brain, the tumour:normal tissue ratio of photosensitizer concentration (as high as 28:1) is probably caused by an inability of the photosensitizer to cross the intact blood-brain barrier in normal areas of brain, whereas this barrier is breached in tumour areas. With the colon, the maximum tumour:normal tissue ratio of 2:1 can be exploited to give selective necrosis only by keeping the tissue concentrations of photosensitizer very close to the photobleaching threshold. In these experiments, Barr *et al.*³ demonstrated that the threshold photodynamic doses were similar for normal and neoplastic colon, and the large difference in the present report between normal and neoplastic pancreas was not seen. This is good evidence that a different mechanism of selectivity is occurring in the pancreas. True selectivity is confirmed by the histological studies showing haemorrhagic necrosis in tumour areas extending to the junction of normal and neoplastic pancreas but with no damage to immediately adjacent normal pancreas (Figure 7).

Schroder *et al.*⁶ studied PDT of BOP-induced pancreatic cancers in Syrian golden hamsters. They used the porphyrin DHE for photosensitization, and light application was carried out 3 h after photosensitizer administration, when the tumour DHE concentration was highest. At this time, all adjacent organs also contained high levels of DHE and these were also exposed to the light. PDT was carried out on seven hamsters, four of which died during the first 4 days, three with intestinal perforations. Histology of the pancreatic tumours revealed carbon debris, indicating hyperthermia, and areas suggestive of photodynamic damage with haemorrhage and necrosis. Animals that survived 1 week demonstrated damage localized to pancreatic tumour tissue with unaffected areas of normal pancreas. Although in the present study gastric lesions were

seen using higher light doses (≥ 50 J) in sensitized normal animals, no perforation occurred. The absence of gastric lesions after PDT of pancreatic tumours probably relates to selectivity of damage by application of light principally to the tumour surface and the smaller light doses (≤ 50 J) used for tumour irradiation. The light dose delivered to the stomach during irradiation is higher when normal pancreas is treated than during tumour light exposure, as tumour bulk shields the stomach, with light flux falling off towards the deep surface of the tumour.

There are several possible explanations for the enhanced selectivity of PDT seen in the pancreas. Mang *et al.*¹³ studied photobleaching kinetics of DHE in normal and neoplastic pancreas. They found that photobleaching in tumours was three times higher than in normal pancreas. Singlet oxygen has been shown to be an active intermediary in the necrosis produced by PDT¹⁴. Mang and colleagues postulated that there may be a singlet oxygen scavenger in normal pancreas that prevented the singlet oxygen produced during PDT from attacking the photosensitizer molecule. If singlet oxygen is involved in photobleaching, the same singlet oxygen scavenging mechanism that protects the photosensitizer from degradation may also protect normal pancreas from damage by PDT. Possible agents for this scavenging role could be glutathione or other intracellular thiols^{15,16} although, in a small preliminary study, we were unable to demonstrate a fall in acid-soluble sulphhydryl content¹⁷ of normal pancreas after PDT (data not presented here). This does not, however, exclude intracellular thiols as protection, because replenishment may occur.

Matthews and Cui¹⁸ have suggested that biochemical differences exist between normal pancreatic acinar cells and an exocrine pancreatic carcinoma cell line (AR4-2J) in responses to PDT using AISPc photosensitization. Photodynamic action inhibited amylase secretion by AR4-2J cells, which contrasted with stimulation of amylase release by normal acinar cells. They suggested that membrane proteins or lipids are inactivated by PDT, leading to inhibition of amylase secretion. Another study¹⁹ (which partly overlapped with the aforementioned one) demonstrated that, although amylase release from isolated pancreatic acini was increased, this was not caused by structural damage, as no changes could be demonstrated on transmission electron microscopy. It was postulated⁸ that the negatively charged AISPc (with a mean of 3.2 sulphonate groups per phthalocyanine molecule) localized to the plasma membrane of intact acini, and little was taken up intracellularly, presumably effectively reducing the photodynamic dose delivered to cells in intact acini.

The present fluorescence microscopy studies on normal pancreas confirmed the localization of AISPc around the edges of acini and on cell membranes but, in addition, there was localization in duct walls. In pancreatic tumours the photosensitizer was localized mainly to stroma, which accords with work carried out on other tumour models using autoradiography²⁰ and fluorescence microscopy⁹. Microscopic localizations of AISPc in normal and neoplastic tissues are related, as the polar photosensitizer molecules tend to accumulate in interstitial spaces, which in tumour tissue are particularly associated with stroma^{21,22}, whereas in normal pancreas transfer across cell and basement membranes is restricted by polarity. The net result of PDT with such photosensitizer molecule distribution is delivery of high photodynamic doses to tumour stroma with light exposure.

Although pharmacokinetic differences exist between tumours and the normal tissues in which they arise, leading to some degree of selective retention of photosensitizers in tumour, it is generally difficult to translate this differential retention into selective necrosis. However, this study has demonstrated greater selectivity of necrosis in BOP-induced pancreatic tumours compared with normal pancreatic tissue than is possible by photosensitizer retention alone. PDT may thus have a role in the destruction of small or strategically placed cancers or as adjuvant therapy when the bulk of tumour has been removed

by other means such as surgery. However, work is required on the effects of PDT on organs closely related to the pancreas, particularly the bile duct, stomach and duodenum, before PDT can be deemed safe to be used in the management of pancreatic carcinoma.

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Duodenogastric reflux enhances growth and carcinogenesis in the rat pancreas

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Surgery for peptic ulcer disease may increase the risk of pancreatic cancer. The effect of duodenogastric reflux on pancreatic carcinogenesis was tested, and changes in the circulating levels of cholecystokinin (CCK) and gastrin were measured. Male Wistar rats ($n = 40$) weighing 250–300 g were randomized to undergo gastrotomy (control) or split gastrojejunostomy (to produce complete duodenogastric reflux) and then to receive azaserine (30 mg/kg/week intraperitoneally) or saline injections for 3 weeks. At 6 months, blood CCK was assayed and the pancreas was excised for quantitative estimation of atypical acinar cell foci (AACF), the precursor lesions of carcinoma. Rats that had undergone split gastrojejunostomy weighed 15–19 per cent less than controls ($P < 0.05$), but their relative pancreatic weight (mg pancreas per 100 g body-weight) was 52–60 per cent greater ($P < 0.001$). Acidophilic AACF occurred only in azaserine-treated rats with duodenogastric reflux. Although plasma CCK concentrations were unchanged, split gastrojejunostomy increased basal and postprandial gastrin levels by 98–175 per cent ($P < 0.05$). Duodenogastric reflux produces sustained hypergastrinaemia and promotes experimental pancreatic carcinogenesis.

Three recent epidemiological studies of the aetiology of pancreatic cancer have shown an increased risk in patients who have previously undergone operations for peptic ulcer disease. Partial gastrectomy and vagotomy with drainage have been implicated^{1–3}, although two studies do not confirm these links^{4,5}. Vagotomy and pyloroplasty stimulates pancreatic growth in rats^{6,7}, possibly as an adaptive response to vagal section or as a result of duodenogastric reflux after pyloroplasty. In rats with complete duodenogastric reflux (obtained by split gastrojejunostomy) the pancreas shows a marked increase in weight with numerous hyperplastic nodules⁸.

Experimental diversion of pancreatobiliary secretion to the mid small bowel causes hyperplasia of pancreatic acinar cells⁹, and long-term pancreatobiliary diversion promotes pancreatic carcinogenesis in the rat–azaserine model¹⁰. In the pancreas, therefore, hyperplasia might precede and predispose to neoplasia, as it does in the large intestine^{11,12}. Cholecystokinin (CCK) and gastrin exert a tropic influence on the exocrine pancreas¹³. Prolonged administration of exogenous CCK increases the number and size of the acidophilic type of atypical acinar cell foci (AACF), the precursor lesion of acinar cell carcinoma^{14,15}, and pancreatobiliary diversion causes a sustained increase in circulating CCK levels⁹.

The hypothesis that duodenogastric reflux enhances experimental pancreatic carcinogenesis was tested using the split gastrojejunostomy model with quantitative estimation of AACF to show early malignant change. Circulating CCK and gastrin levels were measured to determine the intermediary role of these peptides.

Materials and methods

Experimental design

Male Wistar rats ($n = 40$) weighing 250–300 g were housed in groups of five with a 12-h day–night cycle. Standard pelleted rat food (PRD diet; Paterson and the Christopher Hill Group, Porton, UK) and water were freely available. Animals were randomized to undergo either split gastrojejunostomy or gastrotomy and resuture (control). Half of the animals in each group were further randomized after operation to

receive saline or azaserine. Feeding was restarted 12 h after operation. Six months later, after overnight fasting, surviving rats were killed and blood obtained for CCK assay by direct cardiac puncture. The pancreas was excised, trimmed free of fat and lymph nodes, and the wet weight was measured before fixation in 10 per cent buffered neutral formalin. Before immersion in fixative each pancreas was spread out on porous paper to maximize the transectional area for subsequent sectioning.

Basal and postprandial plasma gastrin levels were studied in a further 12 rats: six undergoing split gastrojejunostomy and six controls. Two weeks after operation animals were anaesthetized and a catheter was inserted into the inferior vena cava. Venous blood samples (2 ml) were obtained at 0, 5, 15 and 30 min after a test meal comprising soybean (3 ml), 40 per cent glucose solution (1 ml), water (2 ml) and protein (0.4 g) (Maxipro; Scientific Hospital Supplies, Liverpool, UK). The test meal was introduced through a catheter placed just beyond the pylorus to avoid the direct effect of antral distension on plasma gastrin levels. The blood drawn was replaced by 2 ml saline at each time point to maintain the animals until the end of the study.

Operation

Split gastrojejunostomy was performed by transection of the proximal jejunum 4 cm distal to the duodenojejunal junction, with anastomosis of the afferent limb to the gastric lumen. The efferent limb was anastomosed to the greater curvature of the stomach 1 cm proximal to the pylorus. Control rats underwent gastrotomy, consisting of a 1-cm incision in the greater curvature of the stomach that was immediately resutured. Operations were carried out under light ether anaesthesia. A continuous 6/0 silk suture was used for anastomosis (Figure 1).

Carcinogen

Azaserine (Sigma, Poole, UK) was dissolved in 0.9 per cent normal saline and administered by weekly intraperitoneal injection, starting immediately after operation and continuing for 3 weeks afterwards. The dose was 30 mg/kg/week.

Plasma cholecystokinin assay

Plasma CCK peptides were extracted from cardiac blood samples with C18 SepPak cartridges (Waters, Harrow, UK)¹⁶, and eluates were dried by centrifugal evaporation (Savant, Farmingdale, New York, USA). Details of the assay have been described previously⁹. The sensitivity of variation within assays was 8.2 per cent and between

assays 12.8 per cent. The sensitivity of the assay (defined as the minimal amount of CCK-8 that could be distinguished from zero with 95 per cent confidence) was 0.2 pmol, and the recovery of CCK-8 and CCK-33 through the SepPak and assay procedure was 79 per cent.

Plasma gastrin assay

Venous blood samples for gastrin assay were collected before and after the test meal into tubes containing ethylenediamine tetra-acetic acid. Gastrin levels were measured by standard radioimmunoassay¹⁷ using antiserum G179; changes of 1 pmol/l gastrin could be detected with 95 per cent confidence. The sensitivity of variation within assays was 7 per cent and between assays 15 per cent.

Quantitative estimation of atypical acinar cell foci

Histological sections (5 µm) of the whole pancreas were stained with haematoxylin and eosin, coded and scrutinized 'blind' by light microscopy. AACF were readily identified and classified as acidophilic or basophilic according to established criteria¹⁴. The total area of exocrine pancreatic tissue was measured directly in a single histological section using a VIDS III video image analyser (Analytical Measuring Systems, Cambridge, UK). The same instrument counted both acidophilic and basophilic AACF and measured the transectional areas. Data were processed numerically using the Volugen package (InfoResearch International, Bristol, UK), using an algorithm based on that of Campbell *et al.*¹⁸ and modified by Pugh and colleagues¹⁹. Details of this analysis were described in previous studies¹⁰.

Statistical analysis

Student's *t* test for unpaired data was used for group analysis of plasma CCK and gastrin concentrations. The levels are expressed as mean (s.e.m.). Median values and ranges are quoted for body-weight, pancreatic weight and quantitative estimation of AACF. Statistical analysis of these parameters was performed using Kruskal–Wallis one-way analysis of variance and the Mann–Whitney *U* test.

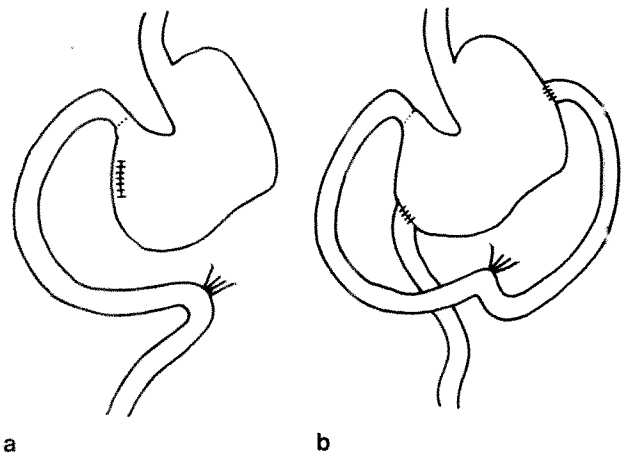


Figure 1 Operative procedures: a gastrotomy (control); b split gastrojejunostomy

Table 1 Body-weight, absolute and relative pancreatic weight

	Treatment			
	Control plus saline	Split gastrojejunostomy plus saline	Control plus azaserine	Split gastrojejunostomy plus azaserine
Body-weight (g)	482 (372–544)	392 (364–491)*	549 (449–637)‡	469 (449–514)§¶
Absolute pancreatic weight (mg)	935 (870–1120)	1255 (850–2190)*	895 (780–1200)	1340 (900–1490)§
Relative pancreatic weight (mg per 100 g body-weight)	196 (168–253)	298 (234–446)†	172 (153–188)‡	274 (190–326)‡

Values are median (range). **P* < 0.05, †*P* < 0.001, ‡*P* < 0.05 (respective group versus control plus saline group); §*P* < 0.05, ¶*P* < 0.001 (respective group versus control plus azaserine group); **P* < 0.05 (split gastrojejunostomy plus azaserine group versus split gastrojejunostomy plus saline group)

Results

Mortality, body-weight and pancreatic weight

Five premature deaths occurred from anastomotic leakage in the animals undergoing split gastrojejunostomy: three with azaserine and two with saline. Healthy survivors were in the following groups: control plus saline (ten); control plus azaserine (ten); split gastrojejunostomy plus saline (eight); and split gastrojejunostomy plus azaserine (seven).

As shown in Table 1, rats that had undergone split gastrojejunostomy weighed 15–19 per cent less than controls. Azaserine-treated animals weighed 14–20 per cent more than their saline-treated counterparts. Azaserine had no effect on absolute pancreatic weight; it reduced the relative weight (mg pancreas per 100 g body-weight) by 13 per cent in controls but had no significant effect in rats undergoing split gastrojejunostomy. By contrast, split gastrojejunostomy markedly increased absolute and relative pancreatic weight (by 34–50 per cent and 52–60 per cent, respectively).

Plasma cholecystokinin

There were no significant differences in circulating CCK concentrations between groups (Table 2). The mean CCK level in control rats studied 6 months after gastrotomy and resuture was 2.52 pmol/l, a value similar to those (2.69–2.93 pmol/l) observed 1–3 weeks after jejunal transection and resuture in a previous study²⁰.

Plasma gastrin (Figure 2)

Basal plasma gastrin levels rose threefold in rats undergoing split gastrojejunostomy; postoperative levels remained 99–129 per cent higher than control values throughout the test. The fall in hormone levels seen in the treated and control groups from 5 min onwards probably represents the dilutional effect of the saline infused to maintain the animals.

Quantitative estimation of atypical acinar cell foci

No pancreatic carcinomas were found. Acidophilic AACF were seen in five of seven rats undergoing split gastrojejunostomy treated with azaserine but in none of the other groups (Table 3). The observed transectional data (foci per square centimetre) and the quantitative stereological analysis of tissue sections

Table 2 Plasma cholecystokinin concentration in rats undergoing split gastrojejunostomy and controls

	Plasma cholecystokinin (pmol/l)
Control plus saline	2.52(0.50)
Split gastrojejunostomy plus saline	4.02(1.00)
Control plus azaserine	3.44(0.58)
Split gastrojejunostomy plus azaserine	2.98(0.22)

Values are mean (s.e.m.)

Results of surgical palliation for cancer of the head of the pancreas and periampullary region

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Between 1977 and 1986, 101 patients underwent surgical bypass for periampullary carcinoma. The hospital mortality rate was 18 per cent and the morbidity rate 43 per cent. Mortality was not influenced by the extent of the tumour. Survival rates at 1, 2 and 3 years were 28, 9 and 4 per cent, respectively. The median survival time was 17 months for localized tumours, 10 months for those that had invaded surrounding tissues, 6 months in the presence of lymph node involvement and 3 months with distant metastasis. The quality of survival was good for most patients with localized tumours but poor for those with parenchymal metastasis, in whom palliation was transient for 85 per cent and effective for less than half of their survival time for 60 per cent. These results suggest that patients with distant metastasis but without impending duodenal obstruction should undergo palliation by endoscopic or percutaneous routes while those with less advanced disease or with duodenal involvement remain candidates for surgical bypass.

Palliation of irresectable adenocarcinoma of the head of the pancreas and periampullary region has evolved with the advent of endoscopic and percutaneous techniques of biliary drainage¹⁻⁶. These two non-operative approaches are most suitable for patients with a short life expectancy or for those with a prohibitive surgical risk. This study reviews a 10-year experience in the surgical treatment of these tumours, before non-surgical methods of palliation became an alternative treatment in this institution. The study also attempts to identify the patients who fared poorly after surgical palliation and who might have benefited from a less aggressive approach.

Patients and methods

The hospital records of 101 consecutive patients who underwent surgical bypass for a periampullary tumour between 1977 and 1986 were reviewed. For the purpose of this study, periampullary carcinoma includes tumours of the pancreas, bile duct, ampulla and duodenum. There were 57 men and 44 women with a median age of 73 (range 47-92) years. Endoscopic or percutaneous drainage was performed only occasionally during this period. Diagnosis was established by preoperative investigation and intraoperative evaluation in every patient and confirmed histologically in 58. Although these tumours arise from different tissues they present with a single clinical picture of a mass in the head of the pancreas that obstructs the flow of bile, pancreatic fluid and/or chyme. The exact origin of the neoplasm was frequently impossible to determine macroscopically and even microscopically: these tumours were therefore referred to as periampullary carcinomas.

Parameters known or thought to predict a poor outcome⁷⁻⁹ were analysed: (1) clinical history - age, duration of symptoms, weight loss, contributing medical conditions; (2) laboratory data - haemoglobin, bilirubin, thrombin time; and (3) tumour extent according to the tumour node metastasis (TNM) system. Group 1 refers to tumours confined to the tissue of origin ($T_1N_0M_0$), group 2 to those invading the surrounding tissues ($T_2N_0M_0$), group 3 to lymph node involvement (any T , N_1M_0) and group 4 to the presence of metastases (any T , any N , M_1). The actual incidence of positive lymph nodes (group 3), however, will have been underestimated, because only macroscopically enlarged nodes were biopsied and no systematic lymph node dissection was carried out around irresectable tumours. Differences in outcome between patients in different stages were compared using the χ^2 test (with Yates' correction when appropriate). Differences were considered significant when $P < 0.05$.

All patients but one were jaundiced at the time of surgery. The type

of bypass was chosen according to intraoperative findings. A choledochoduodenostomy was performed in five patients, a cholecystojejunostomy in 29 (alone in three, with a gastrojejunostomy in 26) and a hepaticojejunostomy in 66 (alone in 21, with a gastrojejunostomy in 45). The patient without jaundice underwent gastrojejunostomy alone. Chemotherapy was not used systematically; it was offered to seven of the youngest patients only. Radiotherapy was used in neither the perioperative nor postoperative period.

Nine patients had localized cancer (group 1). Resection was not attempted because of poor general health: all were grade III or IV according to the classification of the American Society of Anesthesiologists and six patients were >80 years of age. A total of 49 had a tumour invading the peripancreatic tissues (group 2), 17 had regional lymph node invasion (group 3) and 26 parenchymal or peritoneal metastases (group 4). The malignant nature of the tumour was confirmed by tissue diagnosis at the time of surgery in 41 patients (biopsy of the primary site in nine, of lymph nodes in 12 and of metastasis in 20) and/or by autopsy in 41 patients. The diagnosis was confirmed by both surgical biopsy and autopsy in 24 patients. In all, the diagnosis of adenocarcinoma was confirmed in 58 patients.

Operative mortality was defined as death occurring within 1 month of surgery or before discharge, unless the patient had been transferred to a convalescence home free of surgical complications. Follow-up was obtained for 80 of the 83 survivors (96 per cent), from oncology clinic records, from the patients' subsequent admissions, or from their personal physician in the few instances when they did not return to this hospital. There were no survivors at the time of writing. Death was the result of either operative complications (in 18 patients) or tumour progression (in 83). Survival was determined by the Kaplan-Meier method¹⁰.

Quality of life after discharge was assessed using the patient's complaints and symptoms, and the SAKK scale¹¹ (an activity index proposed by the Swiss Group for Clinical Cancer Research used by this oncology service and which is equivalent to the Eastern Cooperative Oncology Group system¹²). SAKK scores of 0 (normal life), 1 (normal activity with acceptable symptoms) and 2 (symptoms present but patient confined to bed for less than half of the daytime) were considered good and scores of 3 (severe symptoms with patient bedridden for more than half of the daytime), 4 (patient bedridden all day) and 5 (death) were considered bad.

A comfort index was defined for each patient by plotting the duration of good palliation (from time of discharge to the moment when the SAKK score rose to 3) against the duration of remaining life (from time of discharge to death). Palliation was considered poor when the index was <50 per cent, intermediate when it was 50-75 per cent and good if >75 per cent. Palliation was considered transient when SAKK scores were good for <75 per cent of the survival time and definitive when they remained good for longer than this.

Results

Operative mortality and morbidity

The operative mortality rate was 18 per cent (18 patients). Mortality was not influenced by the locoregional extent of the tumour (Table 1). Combination of abnormal values of haemoglobin, bilirubin and thrombin time significantly worsened the mortality rate, while age had a less important effect and the duration of jaundice or amount of weight loss had no effect on mortality (Table 1). Postoperative complications occurred in 43 patients (43 per cent). Fatal complications are listed in Table 2. Late complications occurred in 17 patients (21 per cent) after discharge and before they were moribund. There were no differences in the incidence of hospital complications or late complications between the different tumour stages (Table 3).

Table 1 Risk factors and hospital mortality

Factors analysed	No. of patients (n = 101)	Mortality (n = 18)	P*
Intraoperative stage			
Group 1	9	2 (22)	n.s.
Group 2	49	9 (18)	
Group 3	17	3 (18)	
Group 4	26	4 (15)	
No. of abnormal laboratory values†			
0-1	85	10 (12)	0.003
2-3	15	7 (47)	
Age			
< 75 years	60	7 (12)	0.051
≥ 75 years	41	11 (27)	
Duration of jaundice			
< 4 weeks	72	13 (18)	n.s.
≥ 4 weeks	17	4 (24)	
Weight loss			
< 10 kg	63	10 (16)	n.s.
≥ 10 kg	23	4 (17)	

Values in parentheses are percentages. n.s., Not significant; * χ^2 test.

†Abnormal values include: haemoglobin < 10 g dl⁻¹; bilirubin > 12 mg dl⁻¹; and thrombin time < 50 per cent

Table 2 Cause of postoperative death in 18 patients

	No. of patients
Sepsis	6
Peritonitis	2
Cholangitis and liver abscess	1
Pneumonia, lung abscess	2
Acute endocarditis	1
Hepatorenal syndrome	2
Cerebrovascular accident	1
Combined causes*	9

*Gastrointestinal bleed, aspiration pneumonia, respiratory and cardiac failure

Table 3 Hospital morbidity and late complications according to tumour stage

Intraoperative stage	Hospital complications (n = 101)	Late complications (n = 80)
Group 1	2 of 9 (22)	2 of 7 (29)
Group 2	11 of 49 (22)	6 of 39 (15)
Group 3	6 of 17 (35)	4 of 14 (29)
Group 4	6 of 26 (23)	5 of 20 (25)

Values in parentheses are percentages

Postoperative non-fatal complications included gastrointestinal bleeding requiring transfusion in five patients, fever with positive blood cultures in two, delayed gastric emptying requiring gastric decompression for ≥ 10 days in ten and gastrointestinal occlusion in two. General complications included pneumonia in ten patients (some owing to aspiration pneumonia), deep venous thrombosis in two and stroke in one. Seven patients underwent reoperation; all but one died after surgery. These relaparotomies were carried out for abdominal bleeding in three cases, sepsis in two, obstructed gastrojejunostomy (because of a technical mistake) in one and occlusion of the afferent loop in the only patient who survived the second operation. One reoperation was performed because of a bleeding anastomotic ulcer 26 days after the bypass procedure. Two explorations for sepsis revealed one case each of anastomotic leakage and multiple pyogenic liver abscesses.

Readmission was required for late complications in 17 patients. One subphrenic abscess was drained percutaneously 2 months after surgery. Two patients developed cholangitis: one was treated medically, the other by percutaneous drainage. Intestinal obstruction secondary to malignancy occurred in three patients, due to invasion of the gastrojejunostomy in one and of the small bowel in two. One patient (initially in group 1) underwent jejunostomy 10 weeks after operation for malignant obstruction of the afferent loop. In three patients with frequent vomiting, mechanical obstruction was excluded by a gastric swallow. With the exception of patients in the terminal stage of their disease who were not investigated, there were no cases of duodenal obstruction in patients who had undergone a biliary bypass only. Four patients had an upper gastrointestinal haemorrhage that was treated medically; there were two cases of anastomotic ulcers and one case of bleeding gastric varices secondary to thrombosis of the splenic vein. In the last patient, the source of bleeding was not clearly documented. Gastrointestinal bleeding was also reported as a terminal event in four other patients. One had an autopsy that revealed a thrombosed splenic vein with gastric varices, and massive bronchial aspiration of blood. Two patients were readmitted because of unilateral iliofemoral deep venous thrombosis, and one patient suffered a stroke a few weeks after discharge.

Survival and quality of survival

Survival rates at 1, 2 and 3 years were 28, 9 and 4 per cent, respectively. The sole 5-year survivor had a localized adenocarcinoma of the duodenum that was biopsied during the bypass procedure and later confirmed at autopsy. Survival curves according to operative staging are shown in Figure 1. The median survival times were 17, 10, 6 and 3 months for groups 1-4, respectively. There were three survivors at 1 year in group 3 and none in group 4.

Variations in the comfort index according to the operative

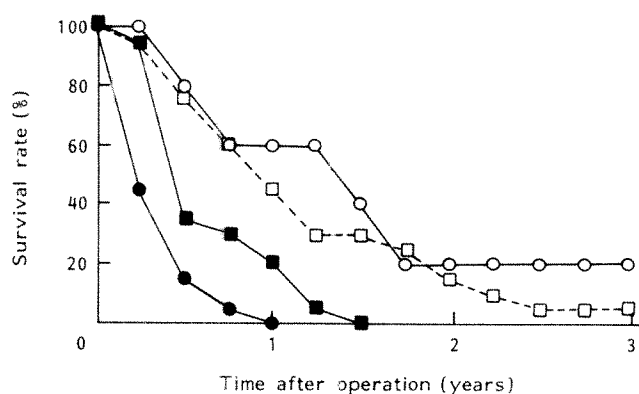


Figure 1 Survival rate according to intraoperative stage. ○, Group 1 (n = 7); □, group 2 (n = 39); ■, group 3 (n = 14); ●, group 4 (n = 20)

Table 4 Quality of palliation according to tumour stage

	No. of patients	Comfort index*		
		<50%	50-75%	>75%
Intraoperative stage				
Group 1	7	0	2	5
Group 2	39	3 (8)	9 (23)	27 (69)
Group 3	14	5 (36)	4 (29)	5 (36)
Group 4	20	12 (60)	5 (25)	3 (15)
Total	80	20 (25)	20 (25)	40 (50)

Values in parentheses are percentages. *This index is the ratio of duration of good palliation (scores 0-2 on the Swiss Group for Clinical Cancer Research (SAKK) scale) to duration of survival since discharge

staging are shown in Table 4. As a whole, patients without parenchymal metastasis had good palliation: 37 of 60 patients (62 per cent) remained active for more than three-quarters of their survival time. On the other hand, most patients (60 per cent) with parenchymal metastasis had effective palliation for less than half of their brief survival and palliation was transient (lasting for less than three-quarters of their remaining life) in 85 per cent of them.

Among the symptoms that impaired the quality of life, pain appeared to be the earliest and most common: it occurred in 60 per cent of patients before they were in a terminal stage. Coeliac plexus blockade with alcohol was performed in six patients, with good but transient results in four. Vomiting occurred in 11 patients and preceded pain in five. One patient underwent reoperation for an afferent loop obstruction. Duodenal obstruction was ruled out by endoscopy and/or gastric swallow in four patients. Further investigations were not performed in the remaining patients because vomiting was sporadic, without the clinical characteristics of obstruction. Jaundice recurred in nine patients and preceded pain in four. Cholangitis (in two patients) and recurrent jaundice (in nine) occurred in four of the 23 survivors with cholecystojejunostomy and in seven of the 54 survivors with hepaticojejunostomy.

Discussion

The results of treatment of periampullary cancer remain disappointing¹³⁻¹⁵. The vast majority of the tumours are aggressive adenocarcinomas, with only a few amenable to resection. Optimal palliation is crucial because these patients have a limited life expectancy and because the symptoms of progressive disease are often unbearable. Prolonged hospital stay, readmission and treatment failure are all equally intolerable.

In the present study the operative mortality rate was 18 per cent for surgical bypass and morbidity affected an additional 25 per cent of patients. These figures are similar to those reported by other teaching institutions^{13,16,17}. The mortality rate directly related to endoscopic or transhepatic insertion of a prosthesis¹⁸⁻²⁰ averages 5 per cent. However, many patients die from their disease within 1 month or are unable to leave hospital after stenting. The hospital mortality rate reaches 15 per cent after such procedures²¹⁻²³ and reflects the patients' diminished state of health and rapid deterioration caused by tumour progression. Analysis of factors associated with higher mortality has failed to identify parameters that could be used reliably to deny a patient surgery^{7,8}. In this study, operative mortality was not influenced by the invasiveness of the tumour, weight loss or duration of symptoms. A combination of anaemia, severe jaundice and impaired coagulation factors was more accurate in predicting increased surgical risks.

Twenty patients experienced very poor palliation (effective palliation lasting for less than half of survival time). Of these patients, 12 already had distant metastases at the time of

surgery. A total of 26 patients had metastases identified at operation, in the liver (20 patients) and/or peritoneal cavity (ten patients). The median survival time was 12 weeks and palliation turned out to be poor for 12 patients and transient (lasting for less than three-quarters of survival time) for 17 of 20 survivors in this group. This is in contrast to patients without parenchymal metastasis who lived longer, with good palliation (lasting for more than three-quarters of their remaining life) in most cases.

Patients at a prohibitive risk for surgery and those with distant metastases but without duodenal obstruction should undergo non-surgical palliation. Prostheses placed endoscopically or percutaneously provide quick recovery and should help patients with advanced disease to spend more of their short life span out of hospital^{6,24,25}. This advantage, however, fades with time owing to complications of the prosthesis (clogging or dislodgement) or subsequent duodenal obstruction²⁶. In our opinion, surgical bypass should be performed when there is duodenal invasion or when no parenchymal metastases are found on radiological investigation (chest radiography, abdominal computed tomography and ultrasonography). Surgery is preferred because histological diagnosis is more easily provided, resectability can be assessed and better palliation can be achieved. Resection for periampullary tumours can be achieved with low mortality rates when performed by expert surgeons, but the cure rate of these resections is often disappointing. Nevertheless, resection still provides the only opportunity of cure and appears to provide the best palliation²⁷.

Histological confirmation of the diagnosis is important. We now biopsy suspected metastases, and operate when none is identified by radiology. Laparoscopy for staging and planning treatment is useful for patients with borderline operative risk and is replacing percutaneous biopsy of the primary tumour in our practice.

The boundaries between surgical palliation and other forms of treatment are still in dispute and may change in the future. At one end of the spectrum, refinements in imaging techniques will increase the number of candidates for non-surgical approaches by detecting metastasis with greater accuracy. At the other end, resection can probably now be contemplated in young low-risk patients (for tumours involving surrounding tissues or adjacent lymph nodes) by surgeons who achieve mortality rates of 5 per cent or below. Between these extremes, surgical bypass represents the best treatment for the majority of patients with periampullary cancer.

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Case report

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Left hepatic vein kinking after right hepatectomy: a rare cause of acute Budd–Chiari syndrome

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Right hepatectomy as classified by Couinaud, also called right hepatic lobectomy, includes resection of segments V, VI, VII and VIII of the liver¹. To fill the right subphrenic space after hepatectomy, displacement of the remaining left lobe of the liver has been proposed². Two cases are described of acute Budd–Chiari syndrome caused by acute occlusion of the left hepatic vein, following prolapse of the left liver into the right subphrenic space.

Case reports

Patient 1

A 75-year-old man developed hepatocellular carcinoma in the right lobe (without cirrhosis) and an associated hydatid cyst of the left lobe. Right hepatectomy and left pericystectomy were performed. After division of the left lateral ligament, the left lobe was placed into the right subphrenic space to fill the residual cavity. From the first day after operation the patient experienced fever, pulmonary oedema, jaundice and massive ascites. Laboratory tests showed leucocytosis, renal insufficiency, raised serum transaminase levels (40-fold) and hepatocellular failure (prothrombin time 30 per cent of normal, factor V level 35 per cent). On the seventh day after operation laparotomy revealed the typical appearances of acute Budd–Chiari syndrome with hepatic ischaemia. The left lobe was replaced in position, which immediately improved the appearance of the liver, and the left lateral

ligament was sutured to the diaphragm. Liver biopsy showed the changes of acute Budd–Chiari syndrome, with areas of ischaemic necrosis, dilatation and congestion of the sinusoids. The postoperative course was marked by abdominal distension, fever and shock. Repeat laparotomy revealed mesenteric venous infarction requiring an ileal resection. The patient died a few hours later from septic shock.

Patient 2

A 55-year-old man presented with a large colonic metastasis in the right lobe of the liver associated with a smaller metastasis on the left. Right hepatectomy was carried out with a wedge resection of the left lobe. After division of the left lateral ligament, the left lobe was placed in the right subphrenic space. During the first 6 h after operation 1.5 litres of ascites were drained and the patient became haemodynamically unstable. Urgent laparotomy was performed. Four litres of ascites were found in the peritoneal cavity, the remaining left lobe was ischaemic and the small bowel was distended with mesenteric venous stasis. The left lobe was replaced in position, causing a marked and immediate improvement in the haemodynamic parameters and restoring a normal aspect to the liver. The round ligament was sutured to the anterior abdominal wall. Pathological examination of a liver biopsy showed the appearances of acute Budd–Chiari syndrome with areas of ischaemic necrosis, dilatation and congestion of the sinusoids. The postoperative course was uneventful.

Discussion

These cases show that swinging the left lobe of the liver to the right to avoid the formation of a subphrenic collection² can cause acute venous outflow occlusion by kinking the left hepatic vein. This complication has very rarely been observed. It can be explained by a combination of three factors, one surgical and two anatomical:

1. Right hepatectomy is usually performed without division of the left lateral ligament¹. In these two patients, partial resection of the left lobe required division of this ligament, allowing the left lobe (disconnected from the diaphragm and the anterior abdominal wall) to twist around the vena cava (Figure 1).
2. One anatomical anomaly that might predispose to abnormal mobility of the left liver is a long extrahepatic segment of the common hepatic venous trunk, which can reach 1.7 cm in some subjects³. Autopsy studies³ have shown that the length of the common left hepatic vein, i.e. the segment

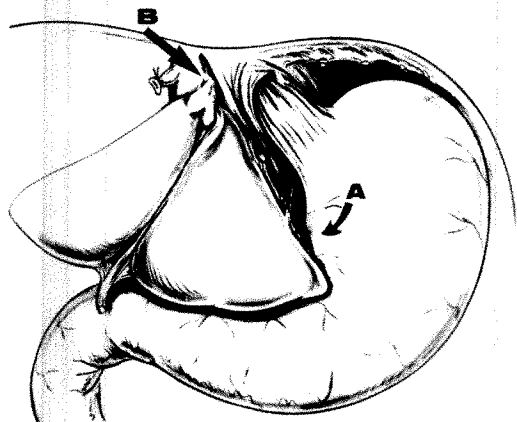


Figure 1 After right hepatectomy, division of the left lateral ligament can be associated with twisting of the left lobe of the liver around the vena cava (arrow A), with resultant kinking of the left hepatic vein (arrow B)

extending from the inferior vena cava to the bifurcation of the middle and left hepatic veins, generally ranges from 0.2 to 0.7 cm.

3. Another relevant anomaly is the absence of functional left accessory dorsal veins. Indeed, ligation of a major hepatic vein without parenchymal resection has been reported without adverse sequelae, illustrating the possibility of venous drainage by collaterals and accessory dorsal veins⁴.

One similar case has been described, but it arose from kinking of the inferior vena cava, which (unlike in the present cases) was dissected during hepatectomy⁵. This risk of hepatic vein obstruction in disconnected liver remnants has also been observed in reduced-size liver transplantation⁶.

In the present patients, the diagnosis of acute Budd–Chiari syndrome caused by acute occlusion of the left hepatic vein was based on the following: (1) massive ascites associated with haemodynamic changes and renal failure directly after operation; (2) operative findings including an ischaemic liver and mesenteric venous stasis; (3) pathological examination of liver biopsies; and (4) an immediate improvement in the haemodynamic parameters and appearance of the liver after repositioning.

Postoperative ascites and shock immediately after right hepatectomy therefore suggest an acute Budd–Chiari syndrome caused by kinking of the left hepatic vein. Venous occlusion might be confirmed by duplex Doppler ultrasonography, if available. Urgent laparotomy is mandatory to replace the left lobe in position. During right hepatectomy displacement of the left lobe must be avoided: either the left lateral ligament should be preserved, or the liver remnant should be fixed to the abdominal wall by means of the round ligament.

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Renal tubular cell injury and serum phospholipase A₂ activity in acute pancreatitis

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Early diagnosis of threatening renal complication is essential for the adequate treatment of acute pancreatitis. Deposition of phospholipase A₂ (PLA₂) in rat renal proximal tubular cells has been observed in experimentally induced acute pancreatitis. The value of measuring the catalytic activity of PLA₂ in serum as an early warning of developing renal tubular cell injury was therefore investigated in a prospective study of 31 consecutive patients suffering from acute pancreatitis. A positive correlation was found ($r = 0.66$, $P < 0.001$) between the highest serum PLA₂ activity, as measured early in the course of acute pancreatitis, and the highest N-acetyl- β -glucosaminidase (NAG):creatinine ratio in the urine. The correlation between the highest serum concentration of immunoreactive pancreatic PLA₂ and the highest urinary NAG:creatinine ratio was weaker ($r = 0.36$, $P < 0.05$). These results indicate that the measurement of the catalytic activity of PLA₂ in serum early in acute pancreatitis may provide a simple test for the detection of threatening renal complication.

Although acute pancreatitis usually runs a benign course, severe attacks with pulmonary and renal insufficiency may prove fatal. Early diagnosis of threatening pulmonary and renal complications is therefore essential for the overall successful treatment of the disease. Measurement of the catalytic activity of phospholipase A₂ (PLA₂) in serum provides a means of early assessment of pancreatic necrosis and pulmonary failure in experimental and human acute pancreatitis¹⁻³. Catalytically active PLA₂ has been considered responsible for both lung changes⁴ and pancreatic necrosis³ in acute pancreatitis in humans.

It has been suggested that disorders in the phagolysosomal system of renal tubular cells play a major role in renal injury in human acute pancreatitis⁵. PLA₂ is rapidly deposited in endocytotic vesicles and lysosome-like vacuoles in rat renal proximal tubular cells both after intravenous injection and in experimental acute pancreatitis, whereas no injected PLA₂ is found in the remaining nephron⁶. The purpose of the present work was to study whether determination of serum PLA₂ activity provides an early guide to the development of renal tubular cell injury in acute pancreatitis in humans.

Patients and methods

Thirty-one consecutive patients admitted with a diagnosis of acute pancreatitis took part in a prospective study. Inclusion criteria were the classical clinical findings of acute pancreatitis (abdominal pain and tenderness, nausea and vomiting), more than a twofold increase in urinary amylase level (in 28 patients the increase was more than threefold) and a history of pain <96 h. The mean age of the patients was 47 (range 26-85) years; 26 were men and five women. There were 17 first bouts of acute pancreatitis and 14 repeat attacks. The aetiology of the disease was alcohol abuse in 23 patients, gallstones in four and unknown in four. Four patients had to be treated in the intensive care unit for 2-30 days, four underwent operation, and one died from a coronary thrombosis.

PLA₂ activity and the serum concentration of immunoreactive pancreatic PLA₂ were determined daily during the first 3 days after admission. Phospholipase activity was measured using radioactive micellar phosphatidylcholine as the substrate⁷. The concentration of pancreatic PLA₂ was measured using a time-resolved fluorescent immunoassay⁸.

The grade of renal tubular cell injury was determined by measurement of the urinary N-acetyl- β -glucosaminidase (NAG):creatinine ratio daily during the first 3 days and every 2 days

thereafter^{9,10}. The NAG:creatinine ratio was used to reduce variability both between and within individuals caused by diurnal variations^{9,10}. NAG was measured according to Maruhn *et al.*⁹ with slight modifications: the total volume of the reaction mixture was 0.4 ml; the final concentration of substrate, 4-nitrophenyl-N-acetyl- β -D-glucosaminide, was 5 mmol/l in 50 mmol/l citrate buffer, pH 4.15; and the reaction was terminated after 15 min at 37°C with 600 μ l 2-amino-2-methyl-1-propanol. Absorbance was read against a reagent blank (physiological saline) and a sample blank (buffer plus sample) at 405 nm. A standard curve for p-nitrophenol was used to determine NAG activity in the samples. Creatinine levels were measured using a kit according to the manufacturer's instructions (Orion, Espoo, Finland).

The BMDP statistical software package (BMDP Statistical Software, Los Angeles, California, USA) was used for parametric linear regression analysis.

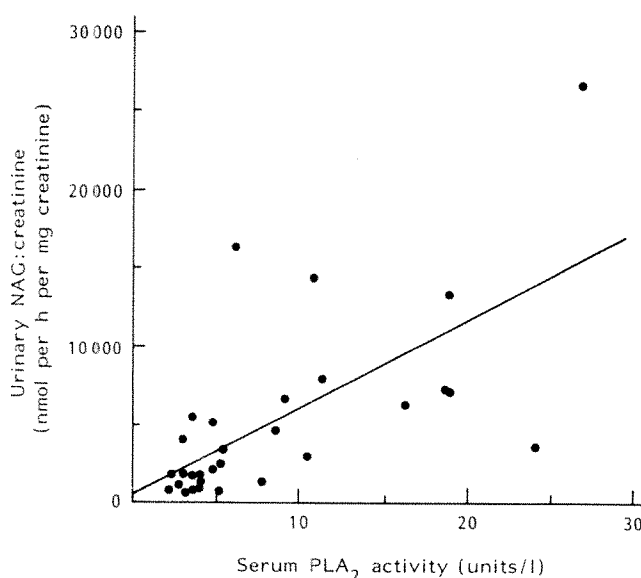


Figure 1 Regression analysis between the highest catalytic activity of phospholipase A₂ (PLA₂) in serum during the first 3 days in hospital and the highest urinary N-acetyl- β -glucosaminidase (NAG):creatinine ratio. $y = 473.48 + 537.79x$ ($r = 0.659$)

Results

PLA₂ activity in serum rose above the normal range¹¹ (0.1–2.1 units/l) in 30 patients during the first 3 days (Figure 1). The urinary NAG:creatinine ratio rose above the normal range¹² (20–100 nmol per h per mg creatinine) in all patients. There was a positive, highly significant, correlation between the highest serum PLA₂ activity and the highest urinary NAG:creatinine ratio ($r = 0.66$, $P < 0.001$). The positive correlation between the highest pancreatic PLA₂ level in serum and the highest NAG:creatinine ratio was less strong ($r = 0.36$, $P < 0.05$).

Discussion

The present study has demonstrated a significant positive correlation between the highest serum PLA₂ activity, as measured early in the course of acute pancreatitis, and the highest urinary NAG:creatinine ratio. This ratio is a very sensitive indicator of the presence and extent of renal tubular cell injury¹⁰. All patients in the present study had an increased NAG:creatinine ratio, which indicates that they had suffered renal damage. This result is in accordance with that of Mock *et al.*⁵, who reported that 90 per cent of patients with acute pancreatitis have increased urinary excretion rates of NAG. Moreover, as the positive correlation between the highest serum PLA₂ activity and the highest urinary NAG:creatinine ratio was highly significant in the present study, it can be concluded that the measurement of PLA₂ activity early in the course of acute pancreatitis provides a simple test for predicting the severity of threatening renal tubular cell injury.

Pancreatic PLA₂ is rapidly deposited in renal proximal tubular cells in experimental acute pancreatitis in the rat, whereas there is no immunoreactive PLA₂ in the remaining nephron⁶. These experimental findings and the results of the present study suggest that catalytically active PLA₂ might play an important role in renal tubular cell injury in acute pancreatitis, although the mechanism of PLA₂ toxicity remains unknown. The incidence of acute renal insufficiency in patients with multiorgan failure seems also to correlate with the serum PLA₂ activity¹³.

Tubular hypoxia resulting from hypovolaemia may play a major role in the development of renal failure in acute pancreatitis¹⁴, although renal failure in this disease may also occur in the absence of hypoxia¹⁵. Hypoxia has been found to increase PLA₂ activity in proximal tubular cells with increased production of toxic lysophospholipids and free fatty acids¹⁶. On the other hand, PLA₂ has been found to cause sustained hypotension and hypoxia by activating the lipoxygenase pathway¹⁷. PLA₂ is also capable of damaging proximal tubular cells under mildly hypoxic conditions *in vitro*^{18,19}. However, the exact actions and interactions of PLA₂ and hypoxia in renal injury in acute pancreatitis remain to be established.

Patients with pancreatitis-associated pulmonary complications have significantly higher serum PLA₂ activities than those without such complications³. No difference was found between these two groups in the serum concentration of pancreatic PLA₂. Similarly, the determination of serum PLA₂ activity differentiated strongly between patients with oedematous and necrotizing acute pancreatitis, whereas no difference was found in pancreatic PLA₂ levels between these two groups³. These authors further indicated that both PLA₂ activity and pancreatic PLA₂ levels are highest during the first 3 days of acute pancreatitis and thereafter both decrease considerably. The present results support the hypothesis that catalytically active PLA₂ is an important factor in the pathogenesis and pathophysiology of acute pancreatitis.

In conclusion, the measurement of serum PLA₂ activity early in the course of acute pancreatitis may provide a simple test for detecting and predicting the severity of threatening renal complication.

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Case report

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Tuberculosis of the pancreas

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The pancreas is rarely affected by tuberculosis in those who have previously harboured the disease. In 1944 Auerbach¹ reported pancreatic involvement in 4.7 per cent of 297 autopsy cases of miliary tuberculosis. Details of two patients who, by coincidence, were admitted to this hospital during the same month (April 1991) are reported below. In each case the diagnosis was made by pancreatic biopsy during exploratory laparotomy.

Case reports

Patient 1

A 29-year-old man with no relevant history was admitted with abdominal pain and weakness. One month earlier he had noticed vomiting and pale stools. Results of physical examination and laboratory tests were normal. Abdominal ultrasonography demonstrated enlargement of the left liver, which was covered by a mass approximately 8 cm in diameter. The portal vein and common bile duct were compressed. At laparotomy there was a hard mass in the head and neck of the pancreas infiltrating the porta hepatis and periaortic tissues. The distal pancreas was normal but there were enlarged lymph nodes nearby. Both the pancreatic mass and the lymph nodes were incised to obtain biopsies for frozen-section examination, and each was reported to be benign.

No further procedure was performed apart from drainage. On detailed histological examination, many granulomatous foci were seen in the peripancreatic fatty tissue and the lymph nodes. Thereafter a tuberculin test was performed and was positive (18 mm) at 48 h. Treatment with isoniazid, rifampicin and pyrazinamide was started, and the patient improved rapidly.

Patient 2

A 57-year-old woman presented with cramping abdominal pain and a history of nausea and vomiting for 2 months. On admission the liver was palpable below the costal margin, and a mass measuring 10 × 10 cm was felt just above the umbilicus. Apart from a raised white blood cell count ($13.6 \times 10^9 l^{-1}$), all laboratory tests gave normal results. Chest radiography showed a bilateral pleural effusion. On abdominal ultrasonography a hypoechoic mass measuring 3.5 × 3.5 cm was detected in the head of the pancreas. Computed tomography demonstrated enlarged lymph nodes showing peripheral enhancement in the region of the lesser curvature of the stomach plus a mass (partly solid and partly cystic) extending from the pancreatic head to the porta hepatis (Figure 1). This multiloculated cystic mass appeared to invade the duodenum and inferior vena cava with loss of margins. Laparotomy confirmed a hard mass in the head and body of the pancreas infiltrating the porta hepatis. The mass was incised for frozen section (result benign) and another biopsy specimen was obtained from the liver; no further procedure was carried out.

On routine histological examination, granulomas were found in both the peripancreatic fatty tissue and the liver, with numerous acid-fast bacilli in the liver. A tuberculin test was positive (20 mm) at 48 h. This patient also responded quickly to triple chemotherapy.

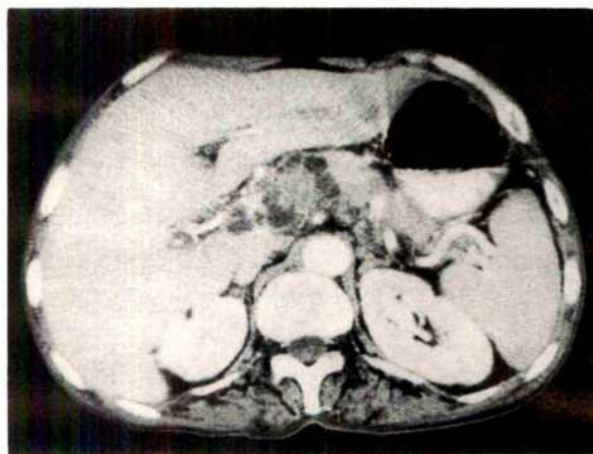


Figure 1 Computed tomographic scan showing a solid and cystic mass in the head of the pancreas in a patient with pancreatic tuberculosis

Discussion

In a review of 300 patients with abdominal tuberculosis from India, Bhansali² did not report a single case in which there was clinical involvement of the pancreas. Pancreatic tuberculosis generally presents with signs of acute or chronic pancreatitis, as biliary obstruction mimicking pancreatic carcinoma, or as a pancreatic abscess^{3,4}.

The diagnosis of tuberculosis of the pancreas is hampered by its rarity. Radiographic evidence of pancreatic calcification usually indicates chronic pancreatitis, although other causes include cystic fibrosis, hyperparathyroidism and kwashiorkor. Computed tomography can also help to delineate the lesion, but alone cannot differentiate between an abscess and a necrotic neoplasm. At laparotomy any material obtained from a pancreatic abscess in a patient who comes from an endemic area should be submitted for histological and bacteriological study to verify the diagnosis of tuberculosis. Pancreatic tuberculosis was not diagnosed in either of the two patients presented until exploratory laparotomy.

A literature search has revealed only two other cases of pancreatic tuberculosis in which the diagnosis was reached during the patient's life^{5,6}.

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Direct surface cooling of the exocrine pancreas in the rat

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Acute pancreatitis is common after accidental hypothermia¹, and almost half of hypothermic patients have high serum amylase levels^{2,3}. Several reports have noted high serum amylase levels and suggest a role for hypothermia in pancreatic injury after major abdominal operations^{4,5}. In these situations, hypothermia may act by systemic effects or by causing local pancreatic injury.

In accidental hypothermia, ischaemia as a result of microcirculatory failure is considered to be a likely causative factor in pancreatic damage, but it is not clear whether local pancreatic hypothermia has an effect on the exocrine pancreas. If this is the case, it may have implications for pancreatic transplantation, in which the preservation solution is always very cold, and the donor pancreas is kept cold before transplantation.

In this study the effects of local pancreatic cooling on the exocrine pancreas were evaluated by determining serum amylase levels, pancreatic water content, pancreatic amylase and cathepsin B content, and the distribution of lysosomal enzymes in acinar cells.

Materials and methods

A group of 56 male Wistar rats weighing about 350 g (Shizuoka Experimental Animals, Shizuoka, Japan) were maintained throughout the study in accordance with the guidelines of the Animal Care Committee of Kyoto University. After a 16-h fast and under general anaesthesia with intraperitoneal pentobarbital (25 mg kg⁻¹), a venous line was inserted into the superior vena cava via the right external jugular vein. Another catheter was placed in the right carotid artery for blood pressure monitoring. A temperature probe was inserted into the rectum. All animals were kept on heating pads at 40°C under overhead lamps. Anaesthesia was continued by intermittent intravenous administration of pentobarbital (10 mg kg⁻¹). Animals were divided into two groups. Group 1 (32 rats) underwent pancreas cooling. The abdomen was opened by an upper midline incision, and 30 ml ice-cold saline in a plastic bag placed on the pancreas from the duodenal loop to the gastric and splenic lobes. This bag was changed every 30 min to keep the pancreas cold. During cooling, the abdomen was closed with small haemostats. Group 2 (24 rats) underwent sham cooling. The abdomen was opened and a bag containing warm saline (38°C) placed in the same position as in group 1. During the experiments, all the animals received intravenous heparin-saline (30 units ml⁻¹) at 0.58 ml h⁻¹.

After 1, 2 or 3 h (group 1, eight rats at each stage; group 2, six rats at each stage) the animals were killed by a large dose of pentobarbital, and the abdomen reopened. After blood sampling for the determination of serum amylase levels, portions (approximately 300 mg) of the pancreas were removed quickly. One specimen was weighed immediately after excision (wet weight) and again after desiccation at 150°C for 48 h (dry weight).

Other portions were homogenized in 4 ml cold phosphate-buffered

A study was carried out to evaluate the effects of direct cooling on the exocrine pancreas. Changes in amylase and cathepsin B release, and in the subcellular distribution of amylase and cathepsin B were measured after 1, 2 and 3 h of direct pancreatic cooling in rats. Cooling for 2 and 3 h caused significant hyperamylasaemia and increased pancreatic amylase content, but minimal histological change. Furthermore, 3 h of cooling caused marked redistribution of cathepsin B activity from the lysosomal fraction to the heavier zymogen fraction, and co-localization of lysosomal and digestive enzymes; amylase and cathepsin B output into pancreatic juice after caerulein stimulation were also reduced. These results show that direct pancreatic cooling impairs exocrine function and implicate lysosomal enzymes in the pathogenesis of pancreatic injury, in agreement with results from other models of experimental pancreatitis.

saline (pH 7.4) containing 0.5 per cent Triton X-100 (Fisher Scientific, Fairlawn, New Jersey, USA) in a Polytron (Brinkmann Instruments, Westbury, New York, USA). The amylase⁶ and cathepsin B⁷ activity and DNA concentration⁸ in the resulting supernatant were measured after low-speed centrifugation (150g, 15 min, 4°C). Pancreatic amylase and cathepsin B contents were expressed as units per mg DNA.

Pancreas from each stage group at each stage was stained with haematoxylin and eosin. The sections were examined by an observer unaware of the treatment. Interstitial oedema, acinar cell vacuolation and inflammatory cell infiltration were graded on a scale of 0-4.

Portions (approximately 700 mg) of the remaining pancreas were homogenized in 6 ml ice-cold 5 mmol l⁻¹ 3-(N-morpholino)propane-sulphonic acid buffer (pH 6.5) containing 1 mmol l⁻¹ MgSO₄ and 250 mmol l⁻¹ sucrose (Sigma Chemicals, St Louis, Missouri, USA). After low-speed centrifugation (150g, 4°C, 15 min) the supernatant was centrifuged. The homogenate was centrifuged twice, at 4°C for 15 min, at 150g and 1300g, to yield a zymogen granule pellet and again for 12 min at 12000g to yield a lysosomal and mitochondrial pellet and the microsomal and soluble fraction. The amylase and cathepsin B activity in each fraction was expressed as a percentage of the total activity to give an index of the subcellular distribution of digestive and lysosomal enzymes in pancreatic acinar cells^{9,10}.

In a fresh and separate group of rats, after 3 h cooling (eight rats) or sham cooling (six animals), the abdomen was opened, and the hepatic duct catheterized to divert bile. The pancreatobiliary duct was cannulated just distal to the duodenum for the collection of pancreatic juice. After 30 min stabilization, caerulein 0.2 µg kg⁻¹ was infused for 1 h and pancreatic juice collected in preweighed microfuge tubes. Amylase and cathepsin B activity in the pancreatic juice was expressed as units kg⁻¹ h⁻¹.

The results are reported as mean (s.e.m.). Differences between groups were assessed using Student's *t* test. For evaluating the histological changes, the Wilcoxon rank sum test was used. Significance was defined as *P* < 0.05.

Results

All rats survived the experiment. Rectal temperatures in the pancreas cooling group (group 1) tended to be lower than in the sham cooling group (group 2), but the differences were not significant at any stage. The mean arterial blood pressure (MABP) showed the same trend, without significant differences and no systemic hypotension. No rats were excluded because of extreme abnormalities of rectal temperature or MABP.

Serum amylase levels in group 1 increased gradually and after 3 h of cooling were significantly higher (mean (s.e.m.) 12(2) units ml⁻¹) than in group 2 (7(1) units ml⁻¹; Figure 1a). Pancreatic water content rose slightly with cooling time, but there were no significant differences between the two groups (Figure 1b).

The pancreatic amylase content in group 1 increased gradually and significantly more so than in group 2, particularly after 2 h (579(46) versus 452(39) units per mg DNA) and 3 h

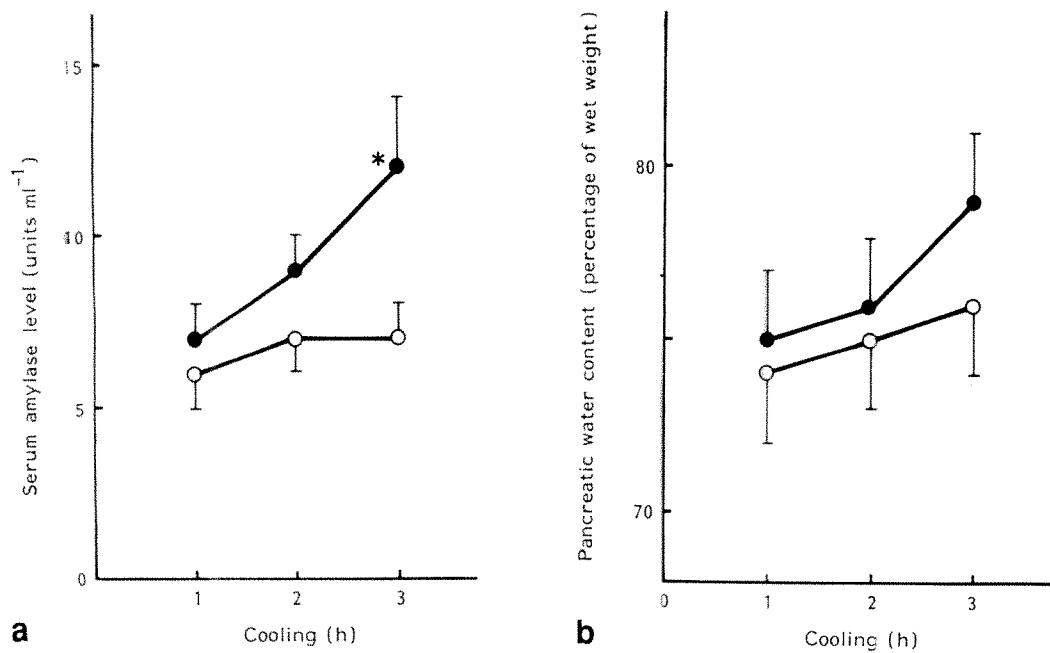


Figure 1 Effect of direct cooling of the pancreas on **a** serum amylase levels and **b** pancreatic water content. ●, Pancreas cooling group (n = 8); ○, sham cooling group (n = 6). *P < 0.05 (Student's t test)

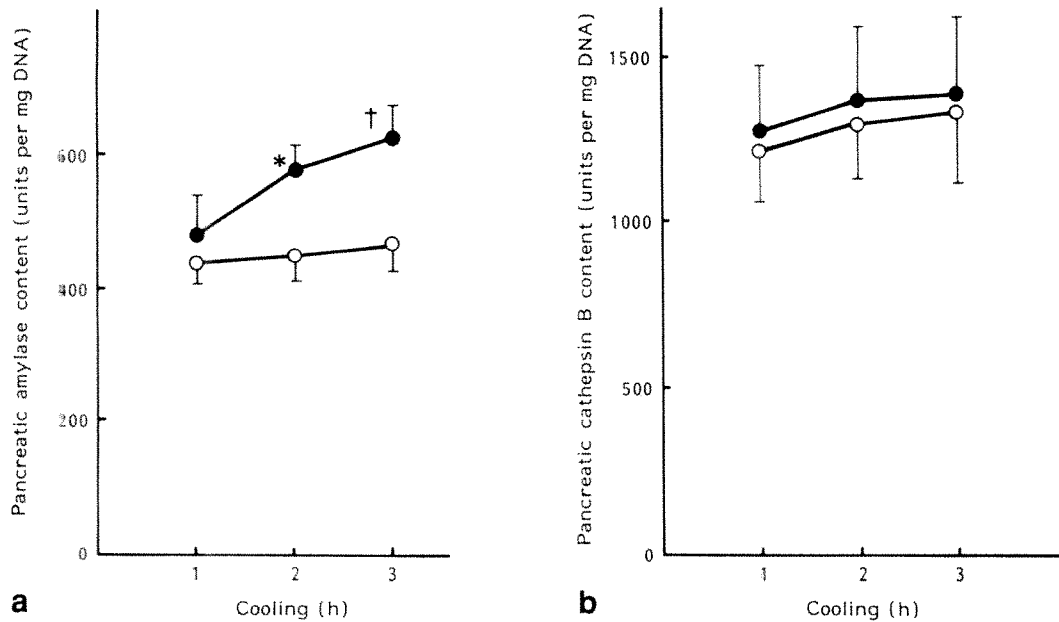


Figure 2 Effect of direct cooling of the pancreas on **a** pancreatic amylase and **b** cathepsin B content. ●, Pancreas cooling group (n = 8); ○, sham cooling group (n = 6). *P < 0.05; †P < 0.02 (Student's t test)

(632(53) versus 471(42) units per mg DNA) of cooling. The cathepsin B content in group 1 was not significantly higher than that in group 2 (Figure 2).

Direct cooling of the pancreas induced no significant changes in interstitial oedema and acinar cell vacuolation. Oedema ranged from 0 to 1 (median 1) at 3 h in group 1 and from 0 to 1 (median 0) in group 2. Acinar cell vacuolation (median 1 (range 0–1) in group 1) and inflammatory infiltration (median 0 (range 0–1) in group 1) were not seen in group 2.

Direct cooling of the pancreas for 3 h caused a significant decrease of amylase activity in the zymogen fraction (29(2) versus 36(2) per cent) and a significant increase in the microsomal and soluble fraction (57(2) versus 48(2) per cent; Figure 3), indicating increased fragility of amylase-containing organelles (zymogen granules) in the process of subcellular fractionation. Cooling of the pancreas for 2 or 3 h caused a significant increase of cathepsin B activity in the zymogen fraction (32(2) and 38(2) per cent versus 26(2) and

27(2) per cent) and a significant decrease in the lysosomal fraction (48(2) and 42(2) per cent versus 56(2) and 54(2) per cent; Figure 4).

Cooling of the pancreas for 3 h caused a significant decrease in the volume of pancreatic juice after caerulein (0.85(0.12) versus 1.6(0.18) ml kg⁻¹ h⁻¹) and a significant decrease in both amylase and cathepsin B output (Figure 5).

Discussion

There have been several reports of the close relationship between hypothermia and acute pancreatic injury^{1–3}, but the exact mechanism of this injury is not clear. In this study, direct pancreatic surface cooling with external whole-body warming was used to evaluate the effect of local pancreatic hypothermia on the exocrine pancreas. This method has less systemic effect than does accidental hypothermia because systemic blood pressure and rectal temperature remain almost normal. Direct

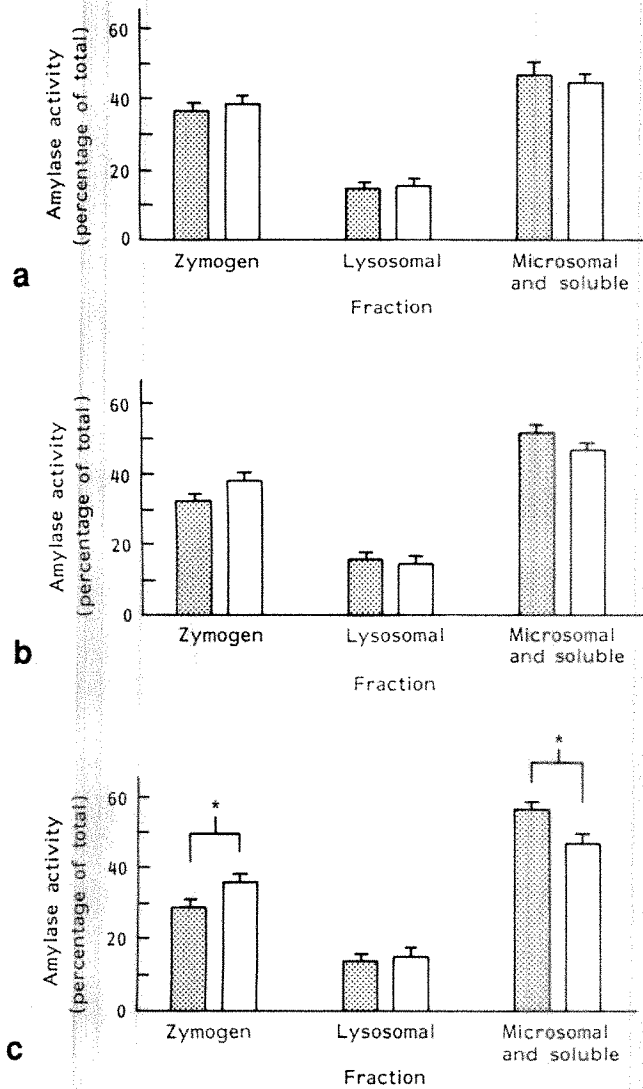


Figure 3 Effect of **a** 1-h, **b** 2-h and **c** 3-h direct cooling of the pancreas on subcellular amylase distribution. $\square$, Pancreas cooling group ($n = 8$); $\square$, sham cooling group ($n = 6$). * $P < 0.05$ (Student's t test)

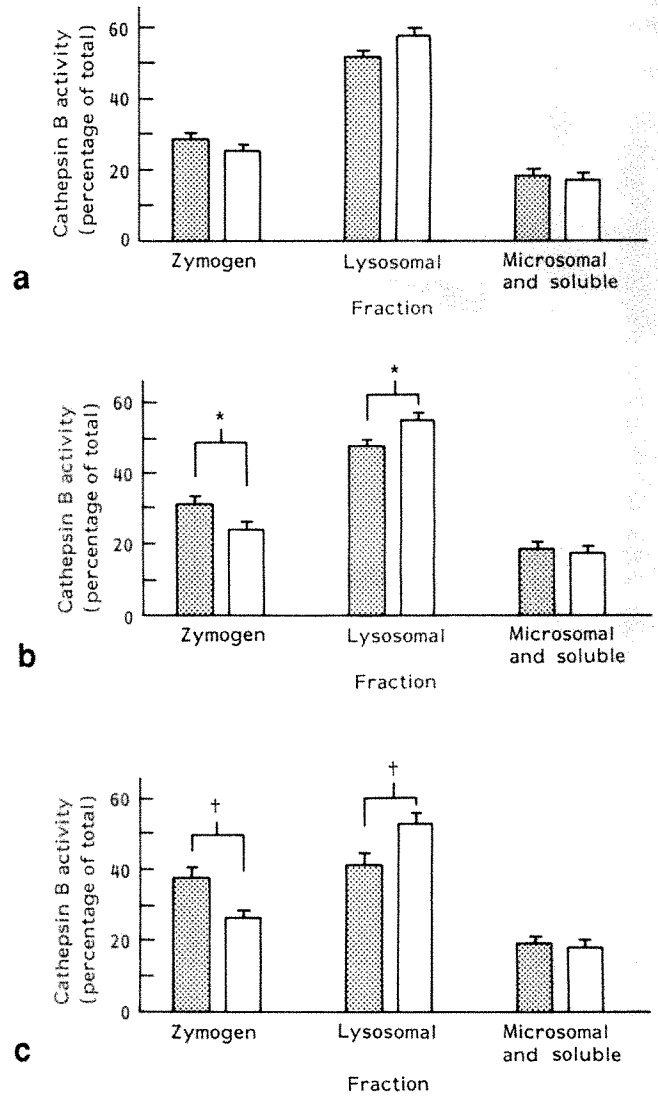


Figure 4 Effect of **a** 1-h, **b** 2-h and **c** 3-h direct cooling of the pancreas on subcellular cathepsin B distribution. $\square$, Pancreas cooling group ($n = 8$); $\square$, sham cooling group ($n = 6$). * $P < 0.05$; $\dagger P < 0.02$ (Student's t test)

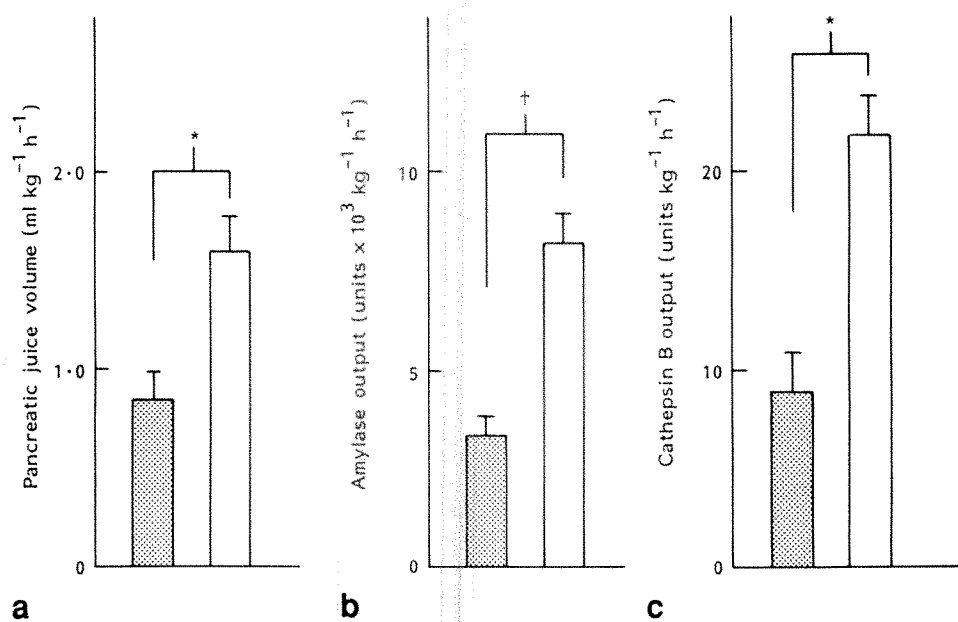


Figure 5 Effect of 3-h direct cooling of the pancreas on **a** pancreatic juice volume, **b** amylase and **c** cathepsin B output stimulated by caerulein $0.2 \mu\text{g kg}^{-1} \text{h}^{-1}$. $\square$, Pancreas cooling group ($n = 8$); $\square$, sham cooling group ($n = 6$). * $P < 0.05$; $\dagger P < 0.01$ (Student's t test)

surface cooling for 3 h caused moderate hyperamylasaemia, a moderate increase in pancreatic water content, moderate accumulation of amylase in acinar cells and minimal histological changes. Cooling caused redistribution of lysosomal enzymes from the lysosomal fraction to the heavier zymogen fraction, indicating co-localization of lysosomal and digestive enzymes.

Pancreatic digestive enzymes and lysosomal hydrolases are generally transported separately from the Golgi apparatus to their own subcellular compartments, condensing vacuoles and lysosomes¹¹⁻¹⁴, and theoretically there should be no co-localization of these two types of enzyme in the same subcellular compartment of acinar cells. However, co-localization of pancreatic digestive and lysosomal enzymes has been reported in caerulein-induced^{15,16}, diet-induced^{17,18}, and duct-obstructed^{19,20} pancreatitis. In these types of experimental pancreatitis, although the ultimate degree of pancreatic injury differs considerably, co-localization of digestive enzymes and lysosomal hydrolases seems to be an important triggering event in the development of acute pancreatitis^{21,22}. Cathepsin B can activate trypsinogen²³⁻²⁶ and trypsin can activate many other key enzymes in acute pancreatitis. In the present study, direct cooling also led to redistribution and co-localization of lysosomal and digestive enzymes.

In recent studies in this unit, lysosomal enzymes were secreted into pancreatic juice both in the basal state and after stimulation by secretin or caerulein. Lysosomal enzyme secretion seems to be important for the maintenance of the normal organization of acinar cells^{19,27}. Direct cooling of the pancreas reduced both cathepsin B and amylase output into the pancreatic juice, which indicates possible accumulation of lysosomal enzymes in the acinar cells.

Since the microcirculation or the core temperature of the pancreas was not evaluated, it is impossible to explain clearly how direct surface cooling injures the exocrine pancreas, which is still innervated and vascularized during the cooling period. Pancreas preserved for transplantation is completely denervated and devascularized and preserved in hypertonic solution. However, there have been reports of hyperamylasaemia or pancreatitis after pancreas transplantation²⁸⁻³⁰, and also of the adverse effects on both the exocrine³¹ and endocrine³² pancreas of too low preservation temperatures.

This study calls attention to methods of organ preservation for pancreas transplantation, because very low temperatures might lead to malfunction of the exocrine pancreas before transplantation, or may predispose the graft to acute pancreatitis.

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Laparoscopic cholecystectomy as a routine procedure for gallstones: results of an 'all-comers' policy

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Cholecystectomy, the most common elective abdominal operation, is safe and effective. Mortality rates may be as low as 0.6 per cent if patients undergoing exploration of the common bile duct are excluded¹. The hospital stay² is usually about 10 days and it may be 4-8 weeks before patients resume work. Much of the postoperative discomfort and disability results from the wound itself. Minimizing the length of the incision may shorten the postoperative hospital stay but the procedure is still painful and requires a lengthy convalescence³.

Laparoscopic cholecystectomy is attended by less postoperative pain and disability than the open procedure and permits earlier discharge from hospital and a more rapid return to work³⁻⁹. Results from specialist referral centres in the USA and continental Europe have been good. The low frequency of acute inflammation of the gallbladder in some reports^{8,10,11} suggests considerable case selection, and raises the question of whether laparoscopic cholecystectomy is equally appropriate for the spectrum of gallbladder disease encountered in unselected patients in the UK.

This report describes 165 consecutive patients with gallstones treated in one surgical department over a period of 15 months. Since the first procedure carried out at this hospital on 5 June 1990, all patients with gallstones have been offered laparoscopic cholecystectomy if considered appropriate.

Patients and methods

A total of 165 patients with symptomatic gallstones scheduled for cholecystectomy were offered laparoscopic removal of the gallbladder under the supervision of one author (M.J.M.) with the understanding that an open operation would be performed if the laparoscopic procedure appeared unfeasible or if a complication developed. Contraindications were advanced pregnancy, multiple abdominal incisions with the expectation of dense adhesions, or the need to carry out an additional procedure requiring laparotomy.

Preoperative endoscopic retrograde cholangiopancreatography (ERCP) was carried out if there was a history of jaundice, if abdominal ultrasonography showed the bile duct to be >7 mm in diameter or if results of liver function tests were abnormal.

The operative technique was based on that evolved by Reddick and Olsen¹². A nasogastric tube was routinely used but bladder catheterization was not performed. A single injection of a cephalosporin was given at the start of the procedure (increased to three doses if the gallbladder was acutely inflamed or contained pus), and heparin (5000

A total of 165 consecutive patients with gallstones were considered for laparoscopic cholecystectomy. Three were excluded. The median age was 52 years and 76 per cent were women. Eighteen patients underwent urgent operation. Laparoscopic cholecystectomy was successful in 160 of the 162 patients (99 per cent). The two failures were the result of dense adhesions and stones in the bile duct. There were no deaths but major complications occurred in three patients: fenestration of the colon sutured laparoscopically; bleeding from a cannulation site and subsequent laparotomy for a strangulated hernia; and subphrenic abscess. There were 13 minor complications, but no bile duct injuries or peritonitis. The median postoperative hospital stay was 1 day. Bile duct stones were present in 14 patients (9 per cent) and were removed by endoscopic sphincterotomy (11 patients), by laparoscopic exploration of the common duct (two) and by conversion to laparotomy (one). These results suggest that laparoscopic cholecystectomy is applicable to the large majority of patients who require elective or urgent cholecystectomy, if appropriate radiological and endoscopic support is available.

units subcutaneously, 12 hourly) was given until the patient was ambulant. All operations were carried out under general anaesthesia. A 10-mm laparoscope was routinely placed through an umbilical incision, but in three patients with scars at the umbilicus, a laparoscope of 5 mm in diameter was inserted through an alternative site. Three further ports were routinely used.

The cystic artery was divided between 6-mm stainless steel clips (LC200; Ethicon, Edinburgh, UK). It was policy to perform intraoperative cholangiography, but a narrow cystic duct or technical difficulties prevented this in 47 patients. The cystic duct was occluded with 9-mm stainless steel clips (LC300; Ethicon - 69 patients), chromic catgut¹³ (21 patients) or absorbable polydioxanone clips¹⁴ (Absolok; Ethicon - 72 patients). The gallbladder was removed from its bed using a neodymium yttrium-aluminium-garnet laser or a diathermy probe. A 4-mm silicone rubber drain was placed in the subhepatic area after the gallbladder had been removed. Absorbable sutures (polyamide or polydioxanone) were used to close the fascia at the umbilicus. The drain was removed the morning after the operation unless there was a reason to retain it (four patients). Patients were allowed home as soon as they were comfortable and mobile.

In two patients the common bile duct was explored laparoscopically under 'screening' using a Dormia basket inserted through the cystic duct.

Results

Three of the 165 patients were not offered laparoscopic cholecystectomy: in two patients another procedure was required that could not be carried out laparoscopically (splenectomy and oesophagectomy) and one patient was thought to be unfit for anaesthesia.

In all, 162 patients were therefore considered for laparoscopic cholecystectomy. The clinical details are shown in Table 1. In 92 patients the gallbladder was functioning (i.e. contained bile) and in 70 it was non-functioning (containing 'white bile', mucus or pus) (Figure 1).

The gallbladder was successfully removed laparoscopically from 160 patients (99 per cent). In two patients the procedure was abandoned because of dense adhesions or the presence of stones in the bile duct.

Most patients left hospital the day after surgery (Figure 2), and 92 per cent were discharged during the first 3 days after operation.

There were no deaths, although 16 complications occurred in 15 patients (9 per cent) (Table 2). Major complications

Table 1 Details of the 162 patients who underwent laparoscopic cholecystectomy

Parameter	Value
Sex ratio (M:F)	39:123
Median age (years)	52 (18-91)
Median body mass index (kg/m ²)*	26.6 (16.9-44.6)
Stones	
Multiple	90
<3	72
Previous abdominal operations	33
Associated medical risk factors	43
Median length of history (months)	14 (1-360)

Values in parentheses are ranges. *Normal range¹⁵ 22-27 kg/m²; calculated using the formula:

Body mass index = $\frac{\text{weight (kg)}}{\text{height}^2 \text{ (m}^2\text{)}}$

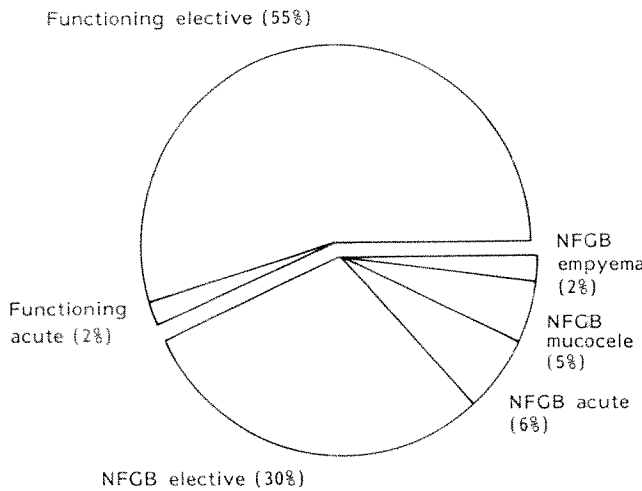


Figure 1 Distribution of patients with functioning and non-functioning gallbladders (NFGB). 'Acute' indicates an operation performed during an acute admission to hospital

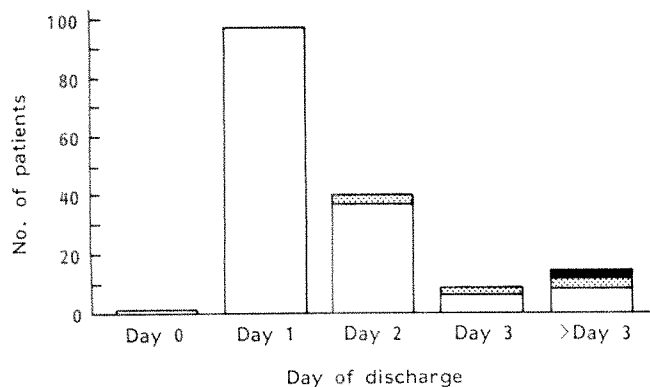


Figure 2 Duration of postoperative hospital stay in 162 patients. □, No complications; ▨, minor complications; ■, major complications

(those which were potentially life-threatening) developed in three patients. In one, a perforation occurred in a densely adherent transverse colon. It was sutured laparoscopically using 3/0 polydioxanone (this patient proceeded to laparotomy because of stones in the bile duct). In another patient the gallbladder was removed successfully, but persistent bleeding from a stab incision was treated by conversion to laparotomy; 8 months after operation this patient was admitted elsewhere and required surgery for a strangulated incisional hernia. The third patient, who had undergone removal of a large acute empyema, developed a subphrenic collection which was aspirated under ultrasonographic control. Minor complications are listed in Table 2. The two patients who had transient

small-volume bile leaks from the abdominal drains were not ill or incapacitated. There were no respiratory complications.

The median operating time was 90 (interquartile range 70-130) min. Factors that significantly influenced the operation time were urgent procedures, gallbladder function, and duration of symptoms (Figure 3). Obesity (body mass index¹⁵) did not influence the duration of operation. Obesity was not a predictor of increased operating time and in severely obese patients (33 patients had a body mass index > 30) median operating time remained at 90 min.

Preoperative ERCP was performed in 43 patients and postoperative ERCP in two. One patient developed mild acute pancreatitis after preoperative ERCP (Table 2). Intraoperative cholangiography was attempted in 123 patients and was successful in 76. Results were normal in 65 patients (86 per cent), showed duct dilatation but no filling defect in seven (9 per cent), and in four (5 per cent) showed unexpected stones in the common duct.

Stones were present in the cystic duct distal to its point of incision in eight patients. Stones were 'milked' upwards using curved forceps in seven patients. In one patient the stone was

Table 2 Complications of laparoscopic cholecystectomy

	n	Action
During operation		
Operative perforation of transverse colon	1	Laparoscopic suture
Bleeding from puncture site	1*	Laparotomy needed
Intraoperative bleed >1 unit	2	Controlled laparoscopically
During hospital stay		
Postoperative bleeding (via drain)	1	Resolved spontaneously
Periumbilical haematoma	1	Laparotomy needed
Bile leakage from drain	2	Resolved in 3 and 5 days
Chest pain	1	Settled, no infarct
Atrial fibrillation	1	Resolved spontaneously
Abdominal bruising	1	Resolved on stopping subcutaneous heparin
After discharge from hospital		
Subphrenic abscess	1	Ultrasonographically guided drainage
Strangulated hernia	1*	Laparotomy needed
Minor wound infection	2	Resolved spontaneously
Complications of ERCP		
Acute pancreatitis following preoperative ERCP	1	Settled in 3 days

ERCP, endoscopic retrograde cholangiopancreatography. *These complications occurred in the same patient

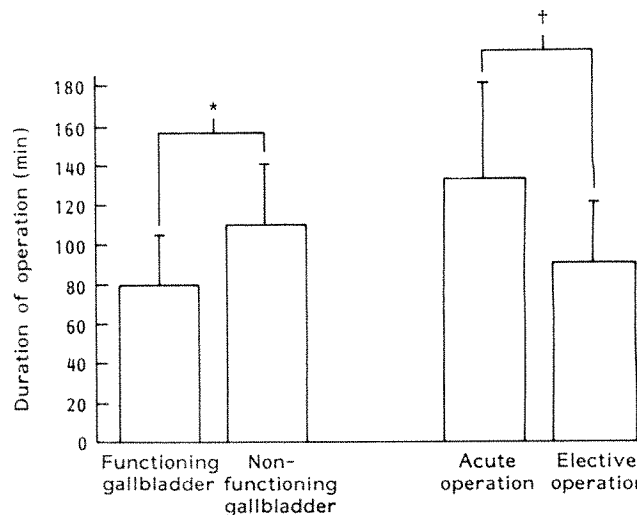


Figure 3 Effect of gallbladder function and acute presentation on the duration of operation. Values are median (upper quartile). *P < 0.0001; †P < 0.005 (Mann-Whitney U test)

Table 3 Method of removal of common duct stones in 14 patients

	n
Preoperative ERCP	10
Postoperative ERCP	1
Laparoscopy	2
Laparotomy	1

ERCP, endoscopic retrograde cholangiopancreatography

pushed into the bile duct and subsequently removed by endoscopic sphincterotomy. Fourteen patients (9 per cent) had stones in the common bile duct (Table 3). All were removed: 11 by endoscopic sphincterotomy, one at laparotomy and two by exploration of the duct using a Dormia basket during the laparoscopic procedure.

Discussion

This experience, using an 'all-comers' policy, suggests that the advantages of laparoscopic cholecystectomy can be safely extended from selected patients to the generality of patients with gallbladder stones who present urgently and electively.

Sixty per cent of patients returned home the day after the procedure and 92 per cent within 3 days, compared with a mean length of stay for open cholecystectomy of 8–12 days in hospitals in the Yorkshire Health Region. Requirements for pain relief were minimal and patients left hospital requiring, at most, small quantities of oral analgesics such as paracetamol, or no analgesics at all. Although analgesic requirements were not prospectively documented in all patients in this study, 40 consecutive patients undergoing the laparoscopic procedure were compared with the most recent 40 patients who underwent cholecystectomy via a transverse incision. The mean administration of opiate for the patients undergoing laparoscopic cholecystectomy was 8 mg compared with 34 mg for the conventionally treated patients. It seems clear that laparoscopic cholecystectomy has major advantages in terms of speed of recovery, comfort and cost, compared with traditional cholecystectomy. The authors agree with Neugebauer *et al.*¹⁶ that it would be difficult to recruit successfully to a randomized trial.

Laparoscopic removal of the gallbladder was successful in patients with acute cholecystitis, thick-walled chronically inflamed gallbladders, mucocele and empyema of the gallbladder. Age and body build did not influence the success of the procedure, although it is the experience of others that patients with gross obesity might require longer instruments. The median duration of the operation was 90 min but includes a 'learning curve' effect.

Some complications, such as conversion to laparotomy to stop bleeding from a cannula insertion site and a strangulated hernia through a cannulation site, were potentially avoidable. Removal of a large thick-walled or stone-laden gallbladder from the abdomen was sometimes a problem, which is conveniently overcome using a 20-mm cannula (GU Manufacturing, London, UK). Others have used ultrasonic or shockwave lithotripsy¹⁷ or a 'bag' introduced into the abdomen, into which the gallbladder is inserted before removal.

Injury to the bile duct has been recorded in up to 1 per cent of published reports^{7,8,10,16}. There was no bile duct injury in this series although great care was taken to keep away from the bile duct during dissection of Calot's triangle. Confirmation of the anatomy was one reason for making intraoperative cholangiography routine. Bile leakage causing peritonitis may occur^{7,8,16} but although bile leakage from the drain occurred in two patients there was no peritonitis. The number of complications from the laparoscopic procedure compared favourably with the morbidity rate from conventional cholecystectomy (6–35 per cent)^{1,2,18}. Many patients were elderly, or had concurrent cardiovascular or respiratory disease. The only significant cardiorespiratory complication was a short

episode of atrial fibrillation. It is not established, however, that laparoscopic cholecystectomy is safer than conventional surgery. There are concerns about increasing partial pressures of carbon dioxide during lengthy procedures¹⁹.

Laparoscopic exploration of the bile duct can be carried out safely and effectively²⁰, although it is technically difficult. Many surgeons therefore attempt to identify and treat common duct stones using ERCP and endoscopic sphincterotomy before laparoscopic surgery. Twenty-seven per cent of the patients in this study underwent preoperative ERCP. This proportion is high, and will probably fall when laparoscopic exploration of the common duct becomes routine. The criteria for preoperative ERCP appear appropriate but complications of ERCP or endoscopic sphincterotomy should be included in any audit of laparoscopic surgery.

Laparoscopic cholecystectomy is one of a variety of minimally invasive techniques for the treatment of gallstones. These include extracorporeal shockwave lithotripsy, percutaneous cholecystolithotomy and minilaparotomy, and endoscopic approaches to bile duct stones. The relative roles of these procedures remain undecided, but patients need to be given informed choices. The clustering of appropriate surgical, endoscopic and radiological skills constitutes an argument for the treatment of gallstones in specialist units.

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Hemihepatic vascular occlusion using intraoperative ultrasonography: a simple technique

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During the past decade, liver surgery has become both safer and more widely practised. The use of the most appropriate strategy to control bleeding holds the key to hepatectomy. Partial hepatic resection under intermittent hepatic inflow occlusion was recently described in patients with chronic liver disease, in whom both hemihepatic vascular occlusion and total hepatic inflow occlusion techniques were performed¹. However, safe encirclement of the right or left hepatic artery and portal vein can still be difficult, particularly in the cirrhotic liver, since the manoeuvre can cause excessive bleeding around the hepatic hilum. Competent use of the intraoperative ultrasonographic probe has become a necessary skill for the hepatobiliary surgeon². This report shows how intraoperative ultrasonography can be used to simplify the above procedures. The importance of obtaining efficient and complete encirclement of the inflow vessels is stressed.

Surgical technique

Cholecystectomy is performed and the liver is mobilized in the usual manner. Thereafter, a T shaped ultrasonographic probe is placed on the liver, and the hepatic hilum is investigated to find the bifurcation of the portal vein. The scan is visualized on a television monitor (model SSD 256; Aloka, Tokyo, Japan). The bifurcation of the portal vein can easily be identified through the liver parenchyma, together with the bile duct and hepatic artery bifurcations. This disposition can be confirmed by preoperative hepatic arteriography and portography, which demonstrate that the right hepatic artery lies in the same sheath as the right portal vein. It is well known to hepatobiliary surgeons that the connective tissue sheath around the hepaticoduodenal ligament normally becomes denser near the porta hepatis³. In the cirrhotic liver, the division of each vessel often brings about extra bleeding and lymphorrhoea. Therefore, encirclement of the entire Glissonian bifurcation (artery, duct and portal vein) is necessary.

The tips of a pair of forceps are applied to the bifurcation while referring to the scan on the monitor (Figure 1), and are moved on the hilum to act as a guide for orientation. A right-angled forceps is then carefully inserted from this point after stripping the surface membrane

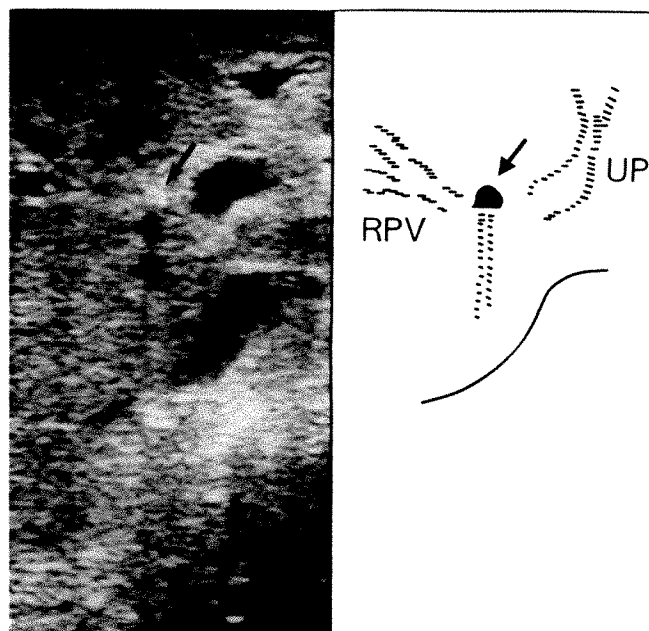


Figure 1 Intraoperative ultrasonography demonstrating the bifurcation of the portal vein, which is actually the Glissonian triad including the hepatic artery and the hepatic duct. The arrow shows the tip of the forceps. RPV, right branch of the portal vein; UP, umbilical portion

on top of the hepatic pedicle adjacent to the liver (both anteriorly and posteriorly), again using the monitor. A branch of the small vessels supplying the caudate lobe may then be divided, which can cause troublesome bleeding; this can be controlled by means of Oxycel (oxidized cellulose; Becton-Dickinson, Franklin Lakes, New Jersey, USA). Thereafter, either the right or the left vascular structures are encircled with an ATOM (polyvinyl chloride; ATOM Medical, Tokyo, Japan) tube of 2.0 or 2.35 mm in diameter. By using this tube, either right or left hemihepatic ischaemia can be achieved, and division of the hepatic parenchyma of the liver started.

Discussion

Intraoperative ultrasonography is extremely useful in performing safe encirclement of the right or left Glissonian triad. The technique shortens the overall operative time and prevents any unnecessary injury to the vessels of the hepatic hilum. Troublesome bleeding and lymphorrhoea are less frequently encountered.

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Management of common bile duct stones using a second-generation extracorporeal shockwave lithotripter

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Fifty-four patients with common bile duct stones (8–36 mm in diameter) that could not be removed after endoscopic sphincterotomy, even with the use of mechanical lithotripsy, underwent extracorporeal shockwave lithotripsy (ESWL) using a Siemens Lithostar. Their median age was 75.5 (range 34–89) years. Patients received 4000–6000 shocks per session over approximately 60 min. Seventeen underwent two sessions and two patients three or more. Thirty-seven patients had one stone, ten had two, and seven had three or more. Spontaneous clearance of fragments occurred in only three patients before further endoscopic retrograde cholangiopancreatography was performed to remove fragments. Stones were removed and ducts cleared endoscopically in 35 patients, giving a total of 38 of 54 patients (70 per cent) with complete duct clearance. Fragmentation in response to lithotripsy was dependent on stone size; the number of stones had little effect. ESWL was well tolerated without any haematological or biochemical abnormality. Computed tomography in the first 20 patients showed no hepatic or pancreatic change after treatment. ESWL combined with endoscopic extraction of fragments is an alternative to surgery when preliminary endoscopic extraction and mechanical lithotripsy have failed.

Endoscopic extraction of common bile duct (CBD) stones is performed in patients who have undergone cholecystectomy and in others considered unsuitable for surgery^{1,2}. In about 10 per cent of patients such stones cannot be removed, usually because a stone is too large to pass through the lower segment of the CBD³. Many techniques, including chemical dissolution⁴ and mechanical⁵, laser^{6–8} and electrohydraulic^{9–12} lithotripsy, have been used with some success to overcome these problems.

The success and safety of extracorporeal shockwave lithotripsy (ESWL) in the treatment of renal calculi is well established¹³. Sauerbruch *et al.*¹⁴ first described this non-invasive technique in the management of stones in the gallbladder and CBD, using a first-generation Dornier (HM3) lithotripter. Several studies have confirmed the success of first-generation ESWL machines in CBD stone fragmentation and duct clearance^{15–17}. Using these machines the patient must be immersed in a waterbath under general or regional anaesthesia. This paper describes the use of a second-generation lithotripter (Lithostar; Siemens, Sunbury-on-Thames, UK) for CBD stones in patients in whom endoscopic extraction had failed or was not appropriate.

Patients and methods

Fifty-four patients were selected for ESWL after endoscopic retrograde cholangiopancreatography (ERCP) had demonstrated CBD stones and endoscopic sphincterotomy (ES) had been performed but stone extraction had failed on at least one occasion. Attempts to assist clearance by mechanical lithotripsy employing crushing baskets (initially Olympus BML 1Q and latterly BML 3Q; Keymed, Southend-on-Sea, UK) were always made. Preliminary investigations included serum liver function tests, urea and electrolytes, and amylase estimations, full blood count, bile culture and urinalysis. In the first 20 patients upper abdominal computed tomography (CT) was performed to ensure a clear path to the CBD without traversing lung. CT was repeated after the procedure in these patients to assess possible gross complications such as hepatic or retroperitoneal haematoma.

The Lithostar produces shockwaves by electromagnetic induction in a water-filled tube. Coupling between the shockhead and the skin

is by a hydrophilic gel pad, which avoids the need for a waterbath. The diameter of the focus of the shockwave, where the energy is at its maximum, is 1.5 cm, but the effectiveness of the shockwave extends 2.5 cm on either side of the focal point in the path of the shockwave (manufacturer's data). The focal length of the shockhead is fixed at 11.5 cm. The technique in ESWL for CBD stones is similar to that used for renal calculi. Stones were localized by biplanar fluoroscopy during pernasal cholangiography and positioned within the focal point of the shockwaves. Because the Lithostar is designed to treat urinary tract stones, and the CBD lies anterior to the renal pelvis, it proved difficult to bring stones into the focal point of the shockhead in all but thin patients in the supine position. This was overcome by treating larger patients in the prone position and recently all patients have been treated in this position.

Two patients who had undergone surgery had cholecystostomy tubes *in situ*. In the remainder (52) external biliary drainage was established by a pernasal catheter inserted at ERCP, to perform cholangiography during and after ESWL, to aspirate bile for culture, to avoid stone impaction and to flush fragments from the ducts after ESWL. Written informed consent was obtained and all patients received a single intravenous dose of piperacillin (2 g) 1 h before ESWL. Initially, local anaesthesia with 20 ml 0.5 per cent lignocaine was used, infiltrating the subcutaneous tissues at the site of contact with the shockhead; more recently, treatments have been given without anaesthesia or analgesia. Up to 6000 discharges at up to 19 kV were given with the patient lying either supine or prone. Initially, patients received light premedication with intramuscular diazepam (10 mg) but this has subsequently proven unnecessary. The procedure takes approximately 60 min.

Haematological and biochemical investigations, bile culture, CT and urinalysis were repeated within 24 h of ESWL in the first 20 patients. Pernasal cholangiography was performed within 48 h to assess fragmentation. The CBD was perfused daily through the pernasal catheter with 2 litres 5 per cent dextrose. Cholangiography was repeated after 2–3 days and if necessary followed by ERCP and further attempts at stone extraction. If the ducts were not cleared then ESWL was repeated if appropriate or a double-pigtail stent inserted to prevent stone impaction, and the patient allowed home. Biochemical investigations were repeated at 48–72-h intervals until discharge from hospital.

From July 1987 to July 1990 a total of 532 patients underwent ERCP and ES for CBD stones. ESWL was performed in 54 patients

(35 women, 19 men), with a median age of 75.5 (range 34–89) years. In three patients aged <60 years, surgery was contraindicated by cerebrovascular disease (one patient), cardiovascular disease (one) and thrombocytopenia (one). Symptoms leading to admission were painless obstructive jaundice (27 patients), obstructive jaundice with biliary pain (23) and biliary pain alone (four). Thirteen patients also had cholangitis and one acute pancreatitis. ES and basket extraction using mechanical lithotripsy was attempted in all patients, ES being possible in 50. Four patients in whom ES was not possible have also undergone ESWL: two had cholecystostomy tubes following complicated surgery (subsequent ERCP had failed due to a Pólya gastrectomy in one and a peripapillary diverticulum in the other); the third patient had a Pólya gastrectomy and ERCP had failed; and the fourth patient had severe thrombocytopenia which precluded sphincterotomy before ESWL, although ES was performed later to remove fragments. Measurements of the size of stones and fragments were made directly from cholangiograms, correcting for magnification using the known diameter of the endoscope.

Attempts were made at ERCP both before and after ESWL to characterize the composition of CBD stones visually from the appearance of extracted fragments.

Stone sizes in patients whose treatment was successful or otherwise were compared using Tukey's critical range test¹⁸.

Results

Patients

Thirty-seven patients (69 per cent) had one stone, ten (19 per cent) had two, and seven (13 per cent) had three or more (Table 1). The mean stone size was 16.1 mm; the largest stone had a diameter ≤10 mm in 11 per cent of patients, 11–20 mm in 64 per cent, 21–30 mm in 17 per cent, and 31–40 mm in 8 per cent. All but four patients had radiolucent stones. Of the four patients with calcified stones, three had dense central calcification and one had calcification peripherally.

The number of ERCP procedures performed before ESWL ranged from one to four (mean 1.6). Thirty patients had undergone cholecystectomy. Fourteen of 24 patients with a gallbladder had gallstones as assessed by ultrasonography of the gallbladder and ERCP. Seventeen patients underwent two ESWL sessions, one had three, and one had four sessions. Stone fragmentation was achieved in a total of 44 patients (81 per cent), with complete duct clearance in 38 (70 per cent), usually after endoscopic extraction. The median interval for CBD clearance after the first ESWL session was 2. (range 1–240) days. The characteristics of the stones have been assessed relative to the success of duct clearance, fragmentation without clearance, and failure of fragmentation (Table 2). The density of stones as measured by CT in the first 20 patients did not appear to predict outcome (Table 3). In only one patient was a pure cholesterol stone found (failed fragmentation). In all others in whom fragments were seen endoscopically, stones were of the mixed type with hard black and soft brown components.

Table 1 Characteristics of common bile duct stones before extracorporeal shockwave lithotripsy

No. of patients (n = 54)	No. of stones	Stone diameter (mm)
37 (69)	1	14–35
10 (19)	2	10–33
7 (13)	≥3	8–23

Values in parentheses are percentages

Table 2 Success of fragmentation and clearance relative to the number of extracorporeal shockwave lithotripsy sessions and stones in the duct

	No. of sessions			No. of stones		
	1	2	≥3	1	2	≥3
Duct clearance (n = 38)	28	9	1	28	8	2
Fragmentation only (n = 6)	2	4	0	2	1	3
No change (n = 10)	5	4	1	7	1	2

Table 3 Density of common bile duct stones in the first 20 patients relative to the outcome of extracorporeal shockwave lithotripsy

	Mean density*
Duct clearance (n = 9)	79 (44–103)
Fragmentation only (n = 5)	98 (66–166)
No change (n = 6)	93 (69–105)

Values in parentheses are ranges. *Measured in Hounsfield units on computed tomography

Table 4 Success of fragmentation and clearance relative to the size of stones

	Mean diameter of stones (mm)	95% confidence interval (mm)
Duct clearance (n = 38)	16.0 (8–33)	14.7–17.5
Fragmentation only (n = 6)	17.1 (10–33)	11.2–26.0
No change (n = 10)	22.5 (16–36)	18.5–27.4

Values in parentheses are ranges. P not significant (clearance versus fragmentation); P < 0.05 (clearance versus no change); Tukey's critical range test¹⁸

Focusing

In 14 patients treated in the supine position, the distance of the stone from the focal point varied from 0 to 3.5 cm. However, in only four of these was there no fragmentation, in two of whom stones were within 1 cm of the focus of the shockwaves. In the 40 patients treated prone, the stone was always at, or within 1 cm of, the focus of the shockwaves.

Fragmentation with clearance

Complete clearance of stones from the ducts was achieved in 28 patients after one session of ESWL and in a further nine after two sessions (Table 2). A second session was required in four patients with solitary stones because no fragmentation had occurred, and to produce fragmentation of remaining stones in five patients with multiple stones. One patient required four sessions to fragment a giant solitary stone (33 mm). The number of discharges varied from 4000 to 6000 per session (mean 5275) with a generator voltage of 14–19 kV. The mean stone diameter was 16.0 (range 8–33) mm; the majority (28 patients) had only a solitary stone (Table 2). The mean (s.d.) fragment size achieved was 5.6(3) mm. Spontaneous clearance of stones occurred in only three patients after nasobiliary perfusion. The remaining 35 patients underwent attempted endoscopic extraction within 1 week of ESWL. The ducts were completely cleared of stones at ERCP within 1 week of ESWL in 28 of 38 patients. In the remaining ten a 7-cm, 7-Fr double-pigtail biliary stent was inserted. In five of these patients the ducts were cleared at a further ERCP session within 2–17 weeks. Four patients required two or three endoscopy sessions to clear the ducts after ESWL. The one patient who needed four ESWL sessions for a solitary stone underwent a total of five ERCP procedures before clearance was achieved. All stents were removed after clearance had been confirmed.

Fragmentation without clearance

Six patients still under treatment have shown fragmentation but complete duct clearance has not yet been achieved (Table 2). Two patients underwent one ESWL session. Four patients had two ESWL sessions: one because the first session had no effect on a solitary stone, one to produce further fragmentation in a solitary stone, and in two to produce further fragmentation in multiple stones. The mean number of discharges was 5100, with a generator voltage of 15–19 kV. Initial stone diameter varied from 10 to 33 (mean 17.1) mm, which was not significantly different from that in those patients in whom the ducts were cleared (Table 4). However, the

Table 5 Complications after extracorporeal shockwave lithotripsy in 54 patients

	Mild	Severe
Biliary pain	0	1
Non-specific pain	2	0
Haematuria	0	1
Skin petechia	10	0
Fever	3	0
Cholangitis	0	1

mean(s.d.) fragment size of 9.2(4) mm was significantly greater than those in the cleared group ($P = 0.02$, Student's t test). As spontaneous duct clearance did not occur, ERCP was performed in all cases. Six patients underwent two follow-up ERCP sessions. When the ducts were not completely cleared at the second ERCP, usually because of large fragment size, the insertion of a biliary stent was attempted. The smaller retained fragments were in patients who had not undergone ES. At present two patients have biliary stents *in situ* and remain symptom-free with no deterioration in hepatic function. One patient with a Pólya gastrectomy had two failed ERCP sessions but remains symptom-free. Elective surgery was performed in one patient who had a cholecystostomy tube *in situ*. Two patients have since died (see below).

Failed fragmentation

Ten patients showed no evidence of stone fragmentation, five after more than one session of ESWL (Table 2). The mean number of discharges was 5275, with a generator voltage of 16–19 kV. The initial stone diameter varied from 16 to 36 (mean 22.5) mm (Table 4). These stones were significantly larger than those in patients in whom the ducts were cleared ($P < 0.05$, Tukey's critical range test). At subsequent ERCP sessions three patients had their ducts cleared with the aid of a mechanical lithotripter. Another duct was cleared using a mechanical lithotripter following infusion of methyl-*tert*-butyl ether. One patient has subsequently died (see below). Four patients had biliary stents inserted and remain well. In one case biliary stenting failed, but this patient remains well despite the presence of a large (36 mm) stone in the CBD.

Complications (Table 5)

Shockwave treatment was tolerated well by most patients. Two treatments were interrupted at 4200 and 4000 discharges because of restlessness of the patient. A further treatment was abandoned after 4100 discharges because of biliary colic. There were no new haematological or biochemical abnormalities that developed after lithotripsy. In particular, there was no elevation of serum amylase concentration. In all patients there was improvement in previously abnormal serum liver function tests, presumably owing to better drainage. Twenty-eight patients had bacterial colonization of the bile before ESWL, but only eight had a positive culture after ESWL. In the first 20 patients no changes were observed on CT of the upper abdominal organs. ERCP carried out after ESWL revealed no mucosal abnormality in the duodenum such as petechiae or haematoma in those patients in whom ERCP was performed shortly (1–4 days) after ESWL. Transient microscopic haematuria occurred in one patient who had an indwelling bladder catheter. Transient fever, resolving in 4 h, developed in three patients. In another patient in whom ESWL had had no effect, acute cholangitis developed after failure to clear the duct or to insert a stent at ERCP. This patient made an uneventful recovery with conservative treatment. One patient developed pancreatitis after initial ERCP. This settled and the patient underwent uneventful ESWL 4 days later. One patient died within 30 days of ESWL: this 73-year-old man succumbed 8 days after ESWL to peritonitis secondary to a perforation of the gallbladder. The gallbladder had not filled during ERCP and was the seat of extensive malignancy. Post-mortem examination revealed no

tissue damage attributable to lithotripsy and the pathologist considered the perforation to be a consequence of the malignant cystic duct obstruction. Two other patients have died. A 77-year-old woman died 5 weeks after ESWL and stent insertion. She developed cholangitis and septicæmia and at post-mortem examination was found to have suffered a perforated bile duct above the level of the stone fragments, possibly caused by the biliary stent. A 75-year-old man also died from myocardial infarction 12 weeks after ESWL.

Discussion

ESWL is now the treatment of choice for renal and ureteric stones^{19,20}. Experience with this technique in the treatment of CBD stones is still limited^{14–17}. All of these studies refer to the use of first-generation lithotriptors (Dornier HM3 and HM4) which require the use of a waterbath and general anaesthesia or heavy premedication. The multicentre study of Sauerbruch *et al.*¹⁴ is the largest reported series to date, with 113 patients being treated with a first-generation lithotripter. General anaesthesia was required in 78 per cent of patients, regional block in 10 per cent and intravenous opiate analgesia in 12 per cent. With second-generation machines, general anaesthesia is not required, which is an advantage in this relatively elderly, high-risk population. One other study²¹ with the Lithostar in 33 patients with CBD stones showed successful clearance after ESWL in 21 at subsequent ERCP.

As with other reports, the clearest factor determining success of fragmentation in the present study was the size of the stones. Experience with urinary tract lithotripsy has shown that large stones may be difficult to fragment. In this study CBD stones of up to 33 mm in diameter showed some disintegration, but the resulting fragments were large. Small stones split to form small fragments while large stones broke up into large fragments, reflecting results from *in vitro* studies²². However, although large fragments may result from ESWL of large stones, these fragments may be amenable to treatment with mechanical lithotripsy. There are other factors that determine fragmentation: the ability to position the stones within the focal point of the shockwaves is an important criterion. This study has shown that even if the stone is not at the focal point of the shockwave, provided it is within the recommended focal zone of the machine, disintegration can still occur. This allows patients to be treated in a supine or prone position.

The number of sessions required for satisfactory disintegration may be a function of the type of machine and depends on the shockwave pressure and the pressure profile at the focal point²³. The first-generation Dornier lithotripter (HM3 – 80 nF model) produces shockwaves up to an energy of 24 kV; this makes the procedure more painful and necessitates the use of general or spinal anaesthesia. The Lithostar has a maximum energy of 19 kV and hence delivers less energy. Fragmentation rates of approximately 90 per cent are achieved with 1500–2000 shockwave discharges using the first-generation Dornier HM3 lithotripter^{15–17}. It has also been suggested that better fragmentation of soft CBD stones may be achieved with the higher energy machines. The present study has shown that this difference in energy and ability to fragment stones can be overcome to some extent by increasing the number of discharges per session. The limited data obtained in this study indicate that the density of stones as measured by CT does not in itself predict outcome (Table 3). Experience with gallstones has suggested that multiple calculi are difficult to fragment²⁴. However, data from the first-generation machines have suggested that, with their large focal zone, several stones can be treated at the same time. The present results have demonstrated that multiple stones in the CBD can be treated successfully with a second-generation machine, although more than one session may be required owing to the smaller focal zone.

In only three patients (6 per cent) was spontaneous clearance of the duct observed within the timespan of the follow-up ERCP

(1 week). This contrasts with rates of 20 per cent¹⁵ and 50 per cent¹⁶ from other studies. The spontaneous clearance rate in the present series may have been higher if the stones had been subjected to more ESWL sessions. To achieve early clearance, endoscopic procedures were preferred, despite patients having undergone ES before ESWL. This early intervention has the advantage of reducing the risk of cholangitis²⁵.

After the use of second-generation ESWL machines, no evidence of hepatobiliary or pancreatic damage was detected by either laboratory tests or CT. Rubin *et al.*²⁶ demonstrated increased size of kidneys following ESWL for renal stones in 9 per cent of patients, intrarenal or subcapsular haematomas in 10 per cent, and fascial plane thickening in 70 per cent. These authors reviewed other publications and concluded that ESWL was remarkably free of significant complications. The present finding of no significant change on CT after ESWL for CBD stones supports that view. Transient haematuria is a well recognized symptom following renal lithotripsy¹³, and one of our patients developed this complication, although this may have been associated with a urinary catheter. Cholangitis occurred in another patient, in whom bile cultures demonstrated *Escherichia coli* which was resistant to the prophylactic antibiotic given. These results confirm both animal and human studies which indicate that ESWL is well tolerated without serious side-effects^{22,23,27}.

Thirty-eight of the 54 patients (70 per cent) had their ducts cleared by combining ESWL with endoscopic extraction. The number with cleared ducts is expected to increase with time as a result of further follow-up of the patients with stents. Many of these patients would have required surgical choledocholithotomy for continuing symptoms and deteriorating hepatic function. Given their age, presenting biliary symptoms and often poor cardiac and respiratory function, the morbidity and mortality rates of such surgery would probably have been higher^{28,29}.

Further experience is needed before the fragmentation of calculi can be predicted satisfactorily and the results of ESWL can be compared with those of other methods of treatment. At present, second-generation ESWL is a valuable adjunctive treatment for CBD stones; it has a low complication rate that compares favourably with elective surgical procedures. The current role of ESWL in the management of CBD stones in our experience is to fragment calculi that cannot be removed following ES or are too large to be snared by the basket of a mechanical lithotripter. Fragmentation allows extraction and mechanical lithotripsy at repeat ERCP with complete duct clearance in 70 per cent of cases. Biliary stents can be used safely to prevent stone impaction in patients with retained stones awaiting further ERCP.

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Operative common bile duct imaging by operative cholangiography and flexible choledochoscopy

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A consecutive series of 108 common bile duct (CBD) explorations was studied to examine the efficacy of routine operative cholangiography and flexible choledochoscopy in the identification of choledocholithiasis. CBD exploration was performed according to the findings of routine operative cholangiography. Nine negative explorations were performed, only one of which would have been avoided had selective cholangiography been employed. Eight patients had unsuspected choledocholithiasis that would have been missed if selective operative cholangiography had been used. Flexible choledochoscopy identified CBD stones on 97 occasions; no additional retained stones were found on subsequent T tube cholangiography. In two cases stones were seen but could not be removed; immediate identification allowed planning for early removal. Flexible choledochoscopy is the most effective method of CBD exploration and should be used in all patients with suspected choledocholithiasis.

Common bile duct (CBD) exploration for stones is required in approximately 12 per cent of patients who undergo cholecystectomy¹. The morbidity caused by the presence and removal of retained CBD stones after cholecystectomy warrants the use of the most effective means of CBD exploration.

The incidence of retained stones after 'blind' CBD exploration is approximately 10 per cent. The introduction of rigid choledochoscopy has reduced this figure to approximately 4 per cent. With the flexible choledochoscope lower retained stone rates can be expected². A review of 21 reports of flexible choledochoscopy has shown a mean retained stone rate of 2 per cent; in six of these studies the rate was zero².

A prospective study was made of a consecutive series of CBD explorations performed using a flexible choledochoscope over a 6-year period (1985-1991) in a district general hospital.

Patients and methods

The study included all patients admitted under one surgical firm for cholecystectomy who underwent CBD exploration.

Indications which would have been used to select patients for operative cholangiography were noted and divided into clinical indications, those from investigations and indications at operation (Table 1). Operative cholangiography was attempted in all patients undergoing cholecystectomy during the study period. The cystic duct was cannulated and three films were taken after injection of successive volumes of 1, 3 and 5 ml to give a total injection of 9 ml 25 per cent Hypaque (Sterling-Winthrop Group, Guildford, UK) contrast medium. The exposure for radiography was calculated individually in each case according to patient anteroposterior diameter measured immediately before operation³.

Exploration of the CBD was performed in the presence of any abnormality of the operative cholangiogram. Abnormal features included a filling defect on one or more films, dilatation of the CBD, absence of flow into the duodenum and absence of filling of both the right and left hepatic ducts. CBD exploration was carried out in most cases by a supraduodenal choledochotomy, although access through the cystic duct, a transduodenal sphincterotomy, or a combination of any of these three approaches, was occasionally used. Stones were removed either by flushing with normal saline, using Desjardin's forceps or by instrumentation via the choledochoscope. After retrieval of stones

Table 1 Indications for selective cholangiography

Clinical

- Current or previous
- Jaundice
- Cholangitis
- Pancreatitis

Investigations

- Abnormal liver function tests
- Aspartate transaminase > 35 units l^{-1}
- Alkaline phosphatase > 120 $\mu\text{mol } l^{-1}$
- Bilirubin > 20 $\mu\text{mol } l^{-1}$
- Ultrasonographic finding of CBD dilatation or CBD stones
- ERCP identification of stones

Operative

- Multiple gallstones
- Dilated cystic duct
- Dilated CBD
- Palpable duct stones

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography

completion choledochoscopy was performed to confirm clearance of the CBD, common hepatic duct and proximal ducts to the level of the second- or third-generation ducts. Particular attention was paid to the identification of the ampulla of Vater. After exploration, the CBD was closed over a standard T tube. Postoperative T tube cholangiography was carried out to confirm operative clearance of the bile ducts.

Results

Over the study period 643 cholecystectomies were performed. CBD exploration was performed in 108 patients and routine operative cholangiography carried out in 105 of these.

Operative cholangiography

In three patients CBD exploration was performed without preceding cholangiography: one was pregnant at the time of surgery and two had obvious palpable calculi within the CBD that had been demonstrated on recent endoscopic retrograde cholangiopancreatography (ERCP).

Of the 105 patients who underwent CBD exploration after

Table 2 Number of cholecystectomies and bile duct explorations during the study period

Procedure	n
Cholecystectomy	643
Exploration of CBD	108 (17)*
Flexible choledochoscopy	106
Positive duct exploration	97 (92)†

Values in parentheses are percentages of *cholecystectomy and †choledochoscopy procedures. CBD, common bile duct

Table 3 Details of 97 positive common bile duct explorations

Mean age (years)	61 (22–93)
Sex ratio (F:M)	59:38
Mode of exploration	
Choledochotomy	83
Cystic duct	6
Combination	8
Choledochotomy and transduodenal sphincterotomy	4
Cystic duct and choledochotomy	2
Cystic duct and transduodenal sphincterotomy	2
Mean time after operation (days)	
T tube cholangiography	8 (2–12)
T tube removal	10 (3–42)
Discharge	11 (5–30)

Values in parentheses are ranges

routine operative cholangiography, selective cholangiography (based on any of the clinical, laboratory or operative findings described) would have been indicated in 96. In the remaining nine patients, who would not have had selective cholangiography, eight had unsuspected CBD stones and one a negative exploration. Of the 96 patients who would have had selective cholangiography, 89 actually had CBD stones.

In the patients with positive indications for selective operative cholangiography, indications in 45 were on clinical grounds. Twenty of these patients were jaundiced at the time of surgery. A further 19 gave a history of preceding jaundice (2 weeks to 10 years earlier), two patients had ascending cholangitis, and four had pancreatitis (two of whom were jaundiced at surgery and required urgent laparotomy and two who had had episodes of pancreatitis 6 and 8 weeks earlier).

Operative cholangiography was indicated in 77 patients after preoperative investigations. Sixty of these had one or more abnormality of liver enzymes or serum bilirubin measured the day before surgery. The 24 jaundiced patients had a mean bilirubin concentration of 126 (range 27–430) $\mu\text{mol l}^{-1}$ and a further seven patients had abnormal bilirubin levels (mean 34 (range 22–56) $\mu\text{mol l}^{-1}$) but were not clinically jaundiced. A total of 23 patients had only one abnormal liver function test result, eight had two abnormal findings and 29 three abnormal results.

Seventy-five patients had indications for selective cholangiography at operation. Only one had positive indications on clinical grounds alone.

Flexible choledochoscopy

Of the 108 patients having CBD exploration, 106 underwent flexible choledochoscopy as part of their operation. Two explorations were performed without choledochoscopy when the instrument was not available. Stones were identified in the biliary tree in 97 of the 106 patients who underwent flexible choledochoscopy (Table 2).

Details of the 97 positive CBD explorations with the flexible choledochoscope are shown in Table 3. A T tube was inserted on 94 occasions. In three instances, after exploration and stone removal via the cystic duct, the duct was ligated and closed without biliary drainage. One patient had the T tube inadvertently removed on the third day after operation but did

not suffer any complications; T tube cholangiography could not be performed.

Retained stones

There were no unsuspected retained stones found on postoperative T tube cholangiography in 91 patients.

On two occasions at choledochoscopy stones were found to lie within the duct system that could not be removed by conventional means. In one, several stones were seen at choledochoscopy to disappear into the proximal biliary ducts and could not be retrieved; transduodenal sphincterotomy was performed. T tube cholangiography confirmed the presence of several small stones and the T tube was left *in situ* for a planned percutaneous extraction at 6 weeks. The T tube fell out at 4 weeks but subsequent ERCP showed a normal duct system. The second patient underwent an acute cholecystectomy; choledochoscopy via the cystic duct showed an impacted stone at the ampulla that could not be dislodged. No further procedure was performed because of intense local inflammation. The duct was drained by a modified T tube inserted through the cystic duct. Postoperative T tube cholangiography confirmed the presence of the stone and the T tube was left *in situ* for a planned percutaneous extraction at 6 weeks. T tube cholangiography at 6 weeks displayed a normal duct system and no stone could be seen. The T tube was removed uneventfully.

Complications

No complications occurred that were attributable to choledochoscopy or operative cholangiography.

Infected bile was present in 38 patients (35 per cent). Two wound infections occurred (one *Staphylococcus aureus*, one *Escherichia coli*). Two T tube track infections occurred (both *S. aureus*). No patient suffered any evidence of bacteraemia on T tube removal.

Four patients suffered right upper quadrant pain on removal of the T tube. This settled spontaneously over 48 h in two patients but required laparotomy, peritoneal lavage and drainage for biliary peritonitis in the other two. One of these had an identifiable leak from the choledochotomy site. Both recovered uneventfully.

One patient died 30 days after surgery from a myocardial infarct.

Discussion

Over 4000 CBD explorations are performed each year in the UK. The techniques employed in duct exploration include 'blind' instrumentation, and rigid and flexible choledochoscopy. A recent review² has highlighted the benefits of flexible choledochoscopy over other methods of duct exploration.

It has been reported that 96 per cent of patients with overlooked bile duct stones required surgery within 5 years of cholecystectomy⁴. It is therefore important to eliminate the possibility of retained common duct stones at the time of cholecystectomy.

The present series of CBD explorations has confirmed the efficacy of this technique in detecting and aiding the removal of CBD calculi. A higher proportion of patients had choledocholithiasis than might have been expected, but we believe this was owing to referrals with diagnosed bile duct stones in accordance with the interest of the senior author. In the early part of the study a standard exploration using Desjardin's forceps to remove stones was carried out before completion flexible choledochoscopy. In the latter part of the study, apart from the removal of stones that appeared on making the choledochotomy, the flexible choledochoscope was used immediately as the exploring instrument and stones removed under direct vision, thus reducing the possibility of trauma to the biliary tree by 'blind' instrumentation.

The success of any form of prevention of retained CBD stones relies in part on the means by which bile duct exploration

is indicated. In this series the indication for exploration relied on the findings of routine operative cholangiography. The technique used in this report has been described elsewhere³ and we believe it is superior to other methods of cholangiography. The initial injection volume of 1 ml contrast medium will not overfill a small duct and after the third injection even a large dilated duct system is filled. Only nine stone-negative explorations (1.4 per cent) were performed in 643 cholecystectomies. This compares favourably with figures of 2–6 per cent reported in recent series^{5–7}. Had selective cholangiography been employed, only one negative exploration would have been avoided.

Biochemical, ultrasonographic and operative indications for cholangiography would have identified 88 of 97 patients with choledocholithiasis. Only one patient with clinical indications alone for operative cholangiography had CBD stones. Eight of 97 CBD stones would have been missed without routine operative cholangiography. The incidence of stones unsuspected on clinical and operative findings that are discovered on routine operative cholangiography has been reported as 3–6 per cent of all cholecystectomies^{8–10}. After selective operative cholangiography the estimated rate of missed common duct stones^{11–13} is 0.2–0.3 per cent. The current series has shown that selective cholangiography would have missed eight CBD stones in 643 cholecystectomies (1.2 per cent), higher than previously estimated. The difference may be due to some stones being passed or remaining clinically undetectable, though it has been shown⁴ that 96 per cent of overlooked CBD stones will require surgery within 5 years.

To assess the effectiveness of the flexible choledochoscope, T tubes were inserted in nearly all patients to allow postoperative T tube cholangiography. Although there is still controversy surrounding the use of T tube drainage after CBD exploration^{14–16}, the only effective method of identifying missed duct stones in all patients after exploration is T tube cholangiography. T tube insertion has the added advantage that if stones are identified the T tube track forms a conduit through which the retained stones may be removed either with the choledochoscope^{17–19} or via a steerable catheter under fluoroscopic control^{20,21}. Neither the high bile leak rate after T tube removal nor the high incidence of bacteraemia on T tube removal previously reported by others¹⁴ was encountered in this series. While we would not maintain that T tube insertion is essential after CBD exploration, it seems sensible that primary closure of the choledochotomy should be performed only after completion flexible choledochoscopy by an experienced operator when the likelihood of stones being missed will be minimal.

Operative choledochoscopy has reduced the incidence of retained CBD stones by permitting a more complete exploration of the biliary system. The flexible choledochoscope possesses features that allow greater manoeuvrability within the duct system, enabling a more thorough examination than can usually be achieved with a rigid choledochoscope. Improved fiberoptic systems now produce images of a similar quality to those of the rigid choledochoscope and the working-irrigation channel allows instrumentation to retrieve stones under direct vision. Retained CBD stones constitute a significant proportion of the workload for an ERCP unit; they accounted for 34 per cent of cases requiring endoscopic sphincterotomy in one series²². It is possible that the techniques described in this series may be used less frequently in the future, as laparoscopic cholecystectomy becomes more widespread, but this report will remain relevant as a modern series of CBD explorations and could act as a standard for comparison with new techniques.

In this study with the use of routine operative cholangiography and flexible choledochoscopy there were no unsuspected retained stones found on T tube cholangiography. In two patients identified bile duct stones were left in place after surgery and the identification of these allowed planning for subsequent removal at an early stage.

Despite the recognized advantages of choledochoscopy at bile duct exploration a recent representative survey of general surgeons in the UK showed that only one-third always used choledochoscopy at CBD exploration and one-third never did so²³.

Flexible choledochoscopy performed in a careful and systematic manner is the most effective method of exploring the bile system for stones. It is a safe and simple procedure and with diligent use should reduce the problem of retained stones to a negligible level.

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Laparoscopic versus open appendicectomy: a prospective evaluation

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A prospective evaluation of laparoscopic surgery for acute appendicitis over a 6-month period is reported. Sixty-five patients with signs and symptoms of appendicitis necessitating surgery were assigned to open (n = 36) or laparoscopic (n = 29) appendicectomy. Thirty-seven patients were female (22 open) and 28 were male (14 open). The median age was 24 (range 14-64) years for open appendicectomy and 18 (range 14-60) years for the laparoscopic procedure. The mean postoperative stay for open operation was 4.8 (range 1-21) days and for the laparoscopic route 2.2 (range 1-11) days ($P < 0.05$). Inflammation was confirmed histologically in 72 per cent of the open cases and in 74 per cent of the laparoscopic cases (P not significant). The wound infection rate was 11 per cent (n = 4) for open and 4 per cent (n = 1) for laparoscopic appendicectomy ($P < 0.05$). The median anaesthesia time was 52 (range 15-90) min for open appendicectomy and 48 (range 20-120) min for laparoscopic surgery (P not significant). After open appendicectomy patients had a median of 5 (range 2-12) intramuscular injections of analgesia compared with a median of 1 (range 0-5) in the laparoscopic group ($P < 0.05$). Two laparoscopic operations were converted to an open procedure. The results suggest that emergency laparoscopic appendicectomy should be explored further as an alternative to open surgery for acute appendicitis.

The mortality rate following surgery for acute appendicitis has declined over the past 60 years to almost zero. Many surgeons question the utility of laparoscopic surgery for acute appendicitis as the appendix can often be removed through a small incision and the degree of trauma to the patient may be equivalent to that of a laparoscopic approach. However, even some patients with a non-inflamed appendix suffer wound infection, prolonged hospital stay and delay in returning to normal activity¹. Laparoscopic removal of the appendix is commonly performed in continental Europe² but laparoscopy has more often been used to aid diagnosis of acute appendicitis¹.

Laparoscopic removal of an acutely inflamed appendix has considerable appeal in that the diagnosis of acute appendicitis can be verified, other pathologies for the cause of right iliac fossa pain can be identified and, if feasible, the appendix removed through a laparoscopic cannula, thus avoiding direct contact of contaminated contents with the abdominal wound. The present study was undertaken to test the feasibility of laparoscopic appendicectomy for acute appendicitis by comparing the outcome for patients undergoing laparoscopic or open surgery.

Patients and methods

From January to June 1991, patients over 14 years of age with clinical signs of acute appendicitis were assigned to open or laparoscopic surgery. Formal randomization was precluded on occasions by instrument availability but not by the time of day at which the operation was performed. Open appendicectomy was performed by a senior registrar or a surgical senior house officer under direct senior registrar supervision. Laparoscopic appendicectomy was performed by a senior registrar (O.J.McA.) with experience in laparoscopic cholecystectomy but no previous training in laparoscopic appendicectomy.

All patients were given perioperative intravenous antibiotics in accordance with each consultant surgeon's usual practice. Antibiotics

were continued for 24 h after operation if the appendix was grossly inflamed or for a longer period if perforated or gangrenous. The open procedure was performed in a routine fashion through a gridiron incision in the right iliac fossa. The skin was closed with interrupted 3/0 nylon sutures.

Laparoscopic appendicectomy was performed by a standard technique. After creation of pneumoperitoneum, a stab incision was made inferiorly at the umbilicus and a 10-mm cannula advanced into the abdominal cavity. A 5-mm cannula was inserted below the right costal margin and a blunt grasping forceps applied to the caecum, which was drawn towards the spleen. After tilting the table to displace small bowel from the pelvis the ovaries were examined. Any free fluid or pus was aspirated at this point. The diagnosis of appendicitis was confirmed and a second 5-mm cannula inserted in the lower left iliac fossa under direct vision, to identify and avoid the inferior epigastric vessels. Using a second grasping forceps through the left iliac fossa cannula, the appendix was grasped along its body and its mesentery clearly displayed. If there was an inflamed retrocaecal appendix, the caecum was retracted cephalad and to the left, and the appendix dissected off the posterior abdominal wall, usually without difficulty. When the mesentery of the appendix had been displayed, the peritoneum was divided and all vessels were coagulated. The appendix was stripped of as much of its mesentery as possible during the dissection: this facilitated its removal through the 10-mm cannula at the end of the operation. When the vessels had been dealt with, a pretied catgut ligature (Ethibinder; Ethicon, Edinburgh, UK) was advanced through the right hypochondrial cannula. The appendix was lassoed and ligated at its base. A second Ethibinder was placed distally along the appendix to prevent spillage of luminal contents after division of the appendix. Care was taken to divide the appendix about 4 mm from the ligature. Magnification on the screen may tempt the surgeon to divide the appendix too close to the caecum, which may cause diathermy injury. After division, the appendix was held by a forceps inserted through the right hypochondrial cannula. The 10-mm telescope was removed and replaced with a 5-mm telescope advanced through the left iliac fossa cannula. The appendix was then withdrawn into the 10-mm cannula, which was extracted with the appendix contained within it. The wounds were infiltrated with 0.5 per cent bupivacaine and closed.

The outcome was assessed using the Mann-Whitney U test and χ^2 analysis as appropriate.

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Table 1 Outcome of open and laparoscopic surgery for acute appendicitis

	Open (n = 36)	Laparoscopic (n = 27)	P
Median postoperative stay (days)*	4 (1-21)	2 (1-11)	<0.05
Median anaesthesia time (min)*	52 (15-90)	48 (20-120)	n.s.
Histological inflammation (n)†	26 (72)	20 (74)	n.s.
Wound infection (n)†	4 (11)	1 (4)	<0.05
Median doses of intra-muscular analgesia*	5 (2-12)	1 (0-5)	<0.05

Values in parentheses are *ranges and †percentages. n.s., Not significant

Results

Sixty-five consecutive patients with signs and symptoms of acute appendicitis underwent either an open (n = 36) or laparoscopic (n = 29) approach. Thirty-seven patients were female, 22 of whom underwent open appendicectomy; 28 were male, 14 of whom underwent open surgery. No patient in either group had undergone previous lower abdominal surgery. The median age was 24 (range 14-64) years for open and 18 (range 14-60) years for laparoscopic surgery. Results are summarized in Table 1.

An equal number of appendices in each group was confirmed histologically to be inflamed. Five appendices in the open and three in the laparoscopic group were either perforated or gangrenous. The median anaesthesia time was the same in the two groups. The mean postoperative stay was 4.8 days for the open procedure and 2.2 days for the laparoscopic procedure ($P < 0.05$).

The wound infection rate was higher after open appendicectomy than after laparoscopic surgery, and the requirement for analgesia greater after the open procedure. One case of wound infection in the laparoscopic group occurred in one of two patients converted to open surgery. In this patient the appendix was perforated at the base, so an Ethibinder could not be applied safely. The second patient was converted early in the study and had a retrocaecal appendix. No subsequent retrocaecal appendix in the laparoscopic group has since been converted.

Two patients underwent laparoscopy only following identification of ovarian pathology. Neither of these patients underwent appendicectomy. The number of retrocaecal appendices in each group was similar (five open, seven laparoscopic).

Discussion

Recent advances in laparoscopic technology have led to a dramatic re-evaluation of the surgical management of visceral pathology. Because of overall improvement in perioperative care during the past century, the mortality rate from acute appendicitis is now nearly zero, but considerable morbidity may occur following open appendicectomy³. Wound infection rates after open appendicectomy have been reported to be as high as 10 per cent, even when the appendix is normal. Following appendicectomy postoperative adhesions have been recorded in as many as 63 per cent of cases⁴, although the implications of adhesions following appendicectomy remain controversial⁵.

Laparoscopic appendicectomy for acute appendicitis has been used in continental Europe^{2,6} over the past 10 years and more recently in Canada⁷. Extraction of the infected appendix through the lumen of the cannula means that at no time is the inflamed organ in direct contact with the wound. This enhances the appeal of laparoscopic removal of the appendix by reducing the risk of wound infection. The present patients were all reviewed 1 month after surgery as it is recognized that

13-66 per cent of infections present after the patient has been discharged⁸.

Laparoscopic removal of the acutely inflamed appendix was successful in all but two cases in the present study. The laparoscopic technique was performed by a trained surgeon with previous experience in laparoscopic cholecystectomy but not in laparoscopic appendicectomy. The time taken to perform the procedure was no less than that taken by a supervised surgeon-in-training performing the open procedure. With increasing experience this time was reduced to <30 min in the last nine patients.

Identification of the inflamed appendix on a colour television monitor requires experience. The negative appendicectomy rate, based on histological confirmation of acute appendicitis, was similar in both groups. This was mainly because in the initial stages a number of normal appendices were removed laparoscopically which by the end of the 6-month period would probably have been correctly identified as not grossly inflamed.

A mean postoperative stay of 4.8 days for open appendicectomy is in agreement with nationally available data⁹. Because of concern over use of the new technique, the surgeons in this study were, if anything, overcautious in suggesting early discharge in the laparoscopic group, but nevertheless these patients had a significantly shorter postoperative stay.

The feasibility of laparoscopic appendicectomy poses a dilemma for the surgeon who encounters the normal appendix at laparoscopy. In cases where other pathology has been identified as the cause of abdominal pain and the appendix appears normal, there appears to be little justification for its removal. However, numerous reports have demonstrated a discrepancy between the surgeon's opinion, the macroscopic appearance of the appendix, and the opinion of the pathologist¹⁰. Lau *et al.*¹¹ in a prospective study found that of 1699 patients studied prospectively as many as 19 per cent thought to have a macroscopically normal appendix were found to have acute appendicitis on histopathological examination and 7.7 per cent diagnosed clinically as having acute appendicitis had normal appendices. Previous or resolved inflammation may be present that is not apparent to the surgeon either at open or laparoscopic operation¹¹. In addition, serosal inflammation does not necessarily imply transmural inflammation (true appendicitis) because the appendix may be secondarily involved by disease elsewhere, for example pelvic inflammation¹². It is a matter of debate, however, whether such specific cases might settle on antibiotics alone.

At laparoscopy clear inspection of the intra-abdominal organs is possible. One example in the present study was the patient who required conversion from an attempted laparoscopic appendicectomy to open operation for perforated appendicitis. This 60-year-old patient had gallstones demonstrated by ultrasonography. At laparoscopy the gallbladder was visualized and found not to be inflamed. Although it was not possible to perform endoscopic removal of the appendix in this patient, laparoscopy allowed appendicectomy through a standard gridiron incision. This patient would otherwise have undergone a midline or paramedian laparotomy with consequent increased risk of local and systemic morbidity after operation.

This study indicates that laparoscopic appendicectomy is feasible for the majority of patients with appendicitis, but a prospective randomized trial with greater numbers is required to ascertain the true role of laparoscopic surgery in acute appendicitis. While laparoscopic appendicectomy significantly reduced the length of hospital stay after operation, the immediate cost of theatre equipment probably increased. This was not addressed prospectively in this study. Until now, laparoscopic equipment has been difficult to obtain and a lack of familiarity by nursing staff, the cost of laparoscopic equipment and its use during elective surgical time for laparoscopic cholecystectomy were all factors that prevented true randomization of patients to laparoscopic versus open surgery. This study, however, was not influenced by the time of day at which the surgery was performed.

Laparoscopic appendicectomy is a feasible option in the management of acute appendicitis in most cases. The present study suggests that it shortens hospital stay and significantly diminishes the risk of postoperative wound infection. Patients were very satisfied with the cosmetic appearance following laparoscopic surgery and this technique seems likely to find a role in the future management of acute appendicitis.

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Temporary abdominal closure: a new product

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Thorough peritoneal toilet is essential in the management of patients with intra-abdominal sepsis. Continuing this beyond the first laparotomy is difficult because neither simple tube drainage^{1,2} nor continuous postoperative lavage^{3,4} is adequate. With multiple laparotomies it may be difficult to close the deep fascia because of the bowel distension found with severe generalized peritonitis. Techniques have been developed to circumvent this problem, but they demand that the patient be ventilated. Insertion of a temporary closure mesh allows a reduction in the requirements for ventilation, improves fluid balance and has subsequently been modified⁵ to incorporate a 'zip' mechanism. The zip laparotomy has become popular but there are potential difficulties in the use of domestic products as temporary biological implants. There is now available a plastic resealable fastener with a non-absorbable, leak-resistant mesh which can be cut to size for any situation. Its use in eight patients (Table 1) is described.

Surgical technique

After completion of the operative procedure and peritoneal lavage, the zip closure (Ethizip; Ethicon, Edinburgh, UK) is prepared for use. Free running of the mechanism should be confirmed and the fastener closed

(Figure 1). The zip is placed over the wound and cut with scissors to the correct shape and size. The fabric portion of the closure is sewn into place along the deep fascia with a strong monofilament suture, and the skin and subcutaneous fat are dressed.

At subsequent planned laparotomies, the abdomen is opened by sliding the fastener. There have been no problems to date with adherence of bowel to the prosthesis. A decision is made at each laparotomy whether to attempt to approximate the fascial edges by reducing the width of the zip. The manufacturers recommend frequent replacement with a new zip but it has not been found necessary to adhere rigidly to this policy. As the primary surgical problem comes under control the width of the wound is decreased by placement of a smaller prosthesis. A policy of not formally closing the wound until two consecutive laparotomies have shown the abdomen to be surgically clean has given good results. These patients have all had the abdomen closed without a fascial defect and none has developed an incisional hernia, although follow-up to date is short (6-12 months).

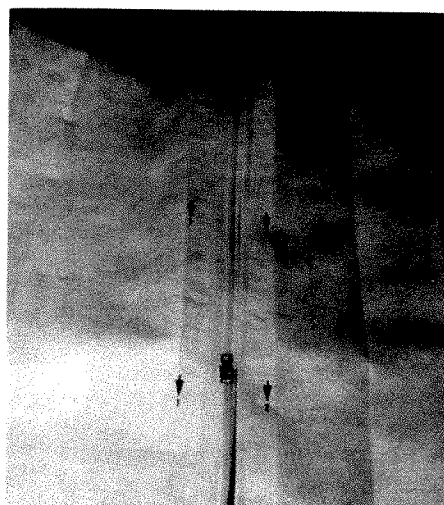


Figure 1 The unfolded prosthesis before trimming and insertion. The two halves can be completely separated if required

Table 1 Details of patients in whom the Ethizip has been used

Patient no.	Diagnosis and operative summary	Age (years)	APACHE II score*	No. of laparotomies	No. of zip changes	Time with zip in place (days)	Outcome
1.	Hepatic lobectomy, small bowel ischaemia, small bowel resection, MSOF	56	26	5	3	12	Alive
2.	Strangulated incisional hernia, infarcted and perforated small bowel, generalized peritonitis, small bowel resection	78	19	4	2	8	Alive
3.	Toxic megacolon, perforation of colon, generalized peritonitis, subtotal colectomy	56	18	5	3	15	Alive
4.	Diverticular disease, perforation of colon, faecal peritonitis, Hartmann's procedure, MSOF	68	21	6	3	18	Alive
5.	Perforated duodenal ulcer with delayed presentation, generalized peritonitis, oversewing of ulcer and omental patch	70	15	4	2	10	Alive
6.	Pólya gastrectomy, duodenal stump leak, intra-abdominal abscess with duodeno-colocutaneous fistula, peritonitis, extended right hemicolectomy with ileostomy, sump drain to duodenum	54	22	8	3	22	Alive
7.	Mesenteric infarction, subtotal small bowel resection with ileostomy, right hemicolectomy with mucous fistula, acute renal failure, short bowel syndrome	64	20	5	2	9	Alive
8.	Dehiscence of colorectal anastomosis, generalized faecal peritonitis, end colostomy, respiratory and renal failure	68	18	4	2	7	Alive

*Score in the 24 h before zip insertion; MSOF, multiple system organ failure

Discussion

This technique avoids the necessity for closing the deep fascia tightly during the acute phase of generalized peritonitis and also avoids *ad hoc* methods of temporary closure. The zip closure prosthesis allows easy access to the peritoneal cavity and facilitates debridement and lavage. Stomas also pose no special problems. Potential problems of manufacturer's liability with the use of dressmaking zips are avoided. The design of the fastener is such that loops of bowel cannot get trapped in its closure mechanism. Because ventilation is not mandatory patients can be managed according to respiratory rather than surgical principles.

No deaths have occurred in this small series but it is not claimed that this method represents a panacea for severe peritonitis. This technique is recommended for closure of the problematic abdomen that may require several operations over a short space of time.

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Role of sequential leucocyte counts and C-reactive protein measurements in acute appendicitis

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The accurate clinical diagnosis of acute appendicitis is difficult, and many techniques have been suggested to improve diagnostic accuracy such as laparoscopy, ultrasonography and barium enema examination. In this study serial total leucocyte counts and serial C-reactive protein (CRP) concentrations in acute appendicitis were measured. The sensitivity and specificity of serial leucocyte counts in acute appendicitis were 92 and 100 per cent, and for CRP concentrations 69 and 75 per cent, respectively. The sensitivity and specificity of serial total leucocyte counts fulfilled the criteria for a diagnostic test. It is suggested that in patients with equivocal clinical findings, clinical observation combined with serial leucocyte counts may improve decision making.

The prevalence of appendectomy in a study population of 5 million has been reported¹ as 16 per cent. Exploration and removal of a non-inflamed appendix after an incorrect diagnosis of acute appendicitis (negative appendectomy) is common²⁻⁴. The clinical diagnosis of acute appendicitis is recognized to be one of the more difficult problems in the management of patients with acute abdominal pain. The accuracy of diagnosis of acute appendicitis has been reported²⁻¹³ to be between 59 and 97 per cent, with negative appendectomy rates^{2-4,6,7,10-14} of between 7 and 38 per cent.

The total leucocyte (white cell) count (WCC) is widely used to aid the diagnosis of acute appendicitis although this is controversial. Of patients with acute appendicitis 79-90 per cent have a raised total WCC^{6,9,13,15-18}. A raised total WCC is a sensitive test for acute appendicitis, but is not diagnostic because of its relatively low specificity^{5,10,19}, and does not contribute to management in patients with unequivocal clinical findings. Some observers have noted that sequential total WCCs may be useful as the total count remains high in acute appendicitis, but falls in conditions not requiring surgical intervention¹⁷, in particular mesenteric adenitis and non-specific abdominal pain (NSAP).

The present study was designed to measure sequential total WCCs and C-reactive protein (CRP) concentrations in acute appendicitis, mesenteric adenitis and NSAP.

Patients and methods

The study was performed prospectively on patients undergoing operation with a preoperative diagnosis of acute appendicitis. Clinical signs and symptoms were recorded on admission and the decision was made to operate or to observe. After informed consent, venepuncture was performed and blood samples obtained for total WCC (Coulter Plus 4 DisPop; Coulter, Florida, USA) and CRP concentration (On-call Chemistry Systems; Barker Instruments, Windsor, UK). Abnormal values were total WCC $>11 \times 10^9 \text{ l}^{-1}$ and CRP $>15 \text{ mg l}^{-1}$. Normal levels of CRP were reported as $<1 \text{ mg dl}^{-1}$.

A second (delayed) blood sample was obtained 4-8 h after admission, and analysed for total WCC and CRP concentration. The initial total WCC was available before surgery; no other haematological results were available to the diagnosing physician. Five patients who underwent operation within 4 h of admission were excluded from the study. Patients who did not come to operation were excluded as they did not have a definitive histological diagnosis to confirm or exclude acute appendicitis.

Operative findings were recorded and inflammation of the appendix, if present, was graded. The appendix was examined histologically only when the operative findings were equivocal.

Statistical analysis was by Student's paired *t* test (parametric data) or by Wilcoxon matched pairs test or Mann-Whitney *U* test (non-parametric data).

Results

In all, 54 patients were entered into the study over a 7-month period. Of these, 24 (44 per cent) were male and 30 (56 per cent) female. The mean age was 20 (range 5-72) years.

Table 1 lists the distribution of pathology found at operation in the 54 patients. A total of 36 patients had acute appendicitis and six had mesenteric adenitis. In six cases no pathology was found; these patients were classified as having NSAP.

The diagnostic accuracy for acute appendicitis was 67 per cent. The results were analysed after exclusion of surgically correctable disease (ovarian cysts, perforated sigmoid diverticula and regional ileitis)¹⁹. The appendix was not significantly inflamed in 22 per cent of patients (negative appendectomy rate) and had perforated in 15 per cent.

Patients were divided into three groups to facilitate analysis of results: acute appendicitis; a surgically correctable condition that was not acute appendicitis; and a final group containing patients with mesenteric adenitis or NSAP.

Of the 54 patients, 20 were initially admitted for observation and delayed review, as the physical findings on admission were thought to be equivocal. The cases admitted for observation included eight patients with acute appendicitis, 11 with mesenteric adenitis and/or NSAP and one with an ovarian cyst.

Table 2 shows the results of the haematological investigations (total WCCs and CRP concentrations).

Statistical analysis was confined to the acute appendicitis

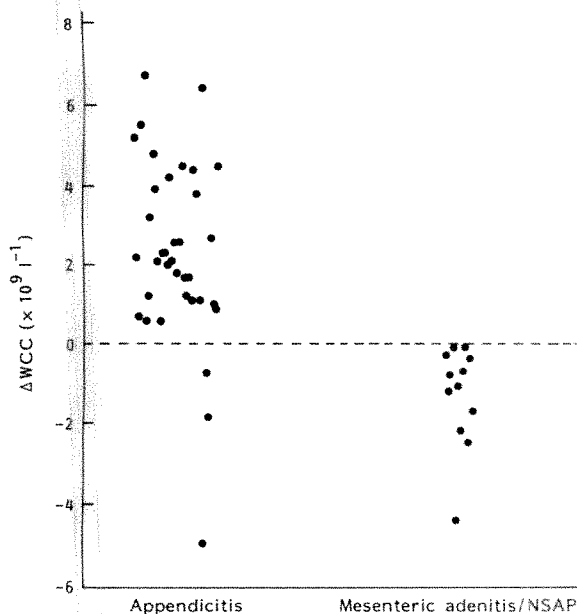
Table 1 Pathological diagnosis at operation in 54 patients with a clinical diagnosis of appendicitis

Finding at laparotomy	No.
Appendicitis	36
Inflamed	26
Gangrenous	3
Perforated	7
Mesenteric adenitis	6
Ovarian cyst	2
Perforated sigmoid diverticula	2
Regional ileitis	2
No apparent cause (non-specific abdominal pain)	6

Table 2 Total leucocyte count and C-reactive protein level in 48 patients with appendicitis, mesenteric adenitis or non-specific abdominal pain

	Appendicitis (n = 36)	Mesenteric adenitis or NSAP (n = 12)
WCC ₁	12.5 (5.5–26.2)	7.2 (4.6–19.3)
WCC ₂	15.1 (7.3–25.9)	6.8 (4.3–16.8)
Δ WCC	2.2 (–4.9 to 6.7)	–1.1 (–4.4 to 0.1)
CRP ₁	1.0 (1.0–22.0)	1.0 (1.0–4.8)
CRP ₂	2.2 (1.0–37.6)	1.0 (1.0–6.2)
Δ CRP	0.5 (–3.0 to 15.6)	0.0 (0.0–1.4)

Values are median (range). WCC, total white cell count expressed in 10^9 l^{-1} ; CRP, C-reactive protein level expressed in mg dl^{-1} ; NSAP, non-specific abdominal pain. Subscripts indicate first and second samples

**Figure 1** Changes in total white cell count (Δ WCC) in patients with acute appendicitis (n = 36) and mesenteric adenitis or non-specific abdominal pain (NSAP) (n = 12) during a period of observation before appendicectomy

group and the mesenteric adenitis/NSAP group. CRP concentrations did not have a normal distribution, and so non-parametric statistics were used for their analysis.

Within the acute appendicitis group, the second total WCCs were significantly greater than the first ($t = -6.25$, 35 d.f., $P < 0.001$). A similar difference was found between the first and second CRP values ($z = -3.84$, $P < 0.001$). In the mesenteric adenitis/NSAP group there was a small but significant fall between the first and second total WCCs ($t = 3.56$, 11 d.f., $P = 0.0045$), but there was no difference between the first and second CRP levels ($z = -1.83$, $P = 0.068$).

Comparison of results between the two pathological groups (i.e. acute appendicitis versus mesenteric adenitis/NSAP) showed that both the first and second total WCCs were significantly different in the two conditions ($z = -3.02$, $P = 0.0025$ and $z = -4.44$, $P < 0.001$, respectively; Mann-Whitney U test). The initial CRP level was not significantly different between the two groups ($z = -1.44$, $P = 0.15$) but the second CRP values were ($z = -2.29$, $P = 0.022$).

The change in total WCC showed an increase in 33 of 36 patients with appendicitis and a fall in all 12 cases of mesenteric adenitis/NSAP (Figure 1). The difference in the change in WCC in the two disease groups was significant ($z = -4.54$,

Table 3 Sensitivity and specificity for the diagnosis of acute appendicitis

	Sensitivity	Specificity
WCC ₁ > $11 \times 10^9 \text{ l}^{-1}$	69	83
WCC ₂ > $11 \times 10^9 \text{ l}^{-1}$	89	83
CRP ₁ > 15 mg l^{-1}	47	75
CRP ₂ > 15 mg l^{-1}	69	75
WCC ₁ > $11 \times 10^9 \text{ l}^{-1}$ + CRP ₁ > 15 mg l^{-1}	42	100
Δ WCC > 0	92	100
Δ CRP > 0	69	75

Values are percentages. WCC, white cell count; CRP, C-reactive protein level. Subscripts indicate first and second samples

$P < 0.001$). The change in CRP was also more often an increase in patients with appendicitis ($z = -2.11$, $P = 0.035$).

Table 3 gives the sensitivity and specificity for WCC and CRP concentration in the diagnosis of acute appendicitis. Values are also given for test combinations.

Discussion

The management of right iliac fossa pain is a difficult clinical problem. A high negative appendicectomy rate has previously been accepted to minimize the risk of appendiceal perforation. Mortality and morbidity rates rise when perforation occurs, with higher incidences of wound infection, intra-abdominal abscess and tubal infertility²⁰. The incidence of appendiceal perforation has been reported^{2–7,13} to be between 4 and 19 per cent.

Removal of a non-inflamed appendix also causes complications. The incidence of intra-abdominal adhesions requiring future surgery is reported²¹ as 0.5–1 per cent, and the risk of developing such adhesions is said to be greater if the appendix removed is not acutely inflamed²².

Laparoscopy, barium enema, ultrasonography and computer-aided scoring systems have all been shown to increase diagnostic accuracy in patients with right iliac fossa pain^{3,4,14,20,23}. However, these techniques are not universally available.

The total WCC is often used in the diagnosis of right iliac fossa pain. Reports of its diagnostic role vary from useful to misleading^{8,24,25}. The total WCC alone is not diagnostic because it has low specificity, although this can be improved by combining the leucocyte count with the differential neutrophil count^{19,24}.

It has been recommended that, if a single total WCC alone is to be used as a diagnostic aid, it should be used only in doubtful cases in conjunction with the physical findings⁸. A normal total WCC should prompt a review of the physical findings, but the latter should take precedence^{9,18}.

In this study, the upper limit of the normal total WCC was taken as $11 \times 10^9 \text{ l}^{-1}$, in accordance with local reference values. (This is at variance with other studies that have taken the upper limit as $10 \times 10^9 \text{ l}^{-1}$ after Hardison²⁶.) In five previous studies^{5,10–12,19} the sensitivity of a raised total WCC in acute appendicitis has been between 60 and 90 per cent, and the specificity between 41 and 84 per cent. These correlate well with the values from this study (69 and 83 per cent respectively).

CRP is an acute-phase protein synthesized by hepatocytes. In this study its upper normal concentration^{27–31} was taken as 15 mg l^{-1} . Four trials^{5,11–13} have reported the sensitivity of elevated CRP concentrations in acute appendicitis to be between 64 and 75 per cent, with a specificity of between 56 and 82 per cent. The sensitivity of CRP concentration in this study (47 per cent) is lower than previously reported, but the specificity (75 per cent) is similar. CRP measurements may be helpful in predicting a cause for pain that is not surgically correctable, so a negative result may be of greater assistance than a positive one.

The use of serial measurements in the diagnosis of right iliac

fossa pain is an extension of the policy of clinical observation of patients with equivocal physical findings. Regular re-examination of patients may aid diagnosis as may serial haematological measurements. The total WCC has been shown to give an indication of the severity of appendiceal inflammation³²; as inflammation proceeds the count rises³³. CRP levels also follow disease progression, with higher levels recorded in more advanced disease¹¹.

Two previous studies of serial total WCCs in acute appendicitis have reported conflicting findings. English *et al.*¹⁷ showed that counts remained high in patients with acute appendicitis but fell in those with NSAP. Conversely, Lyons *et al.*⁶ concluded that serial counts are of no value even in equivocal cases.

The results from this study give a 92 per cent sensitivity and a 100 per cent specificity for serial total WCC measurements in acute appendicitis. All 12 patients in the mesenteric adenitis/NSAP group showed a fall in the second count, whereas all but three patients with acute appendicitis showed a rise in the second sample. All three patients in whom the second total WCC fell had a perforated appendix, which is a well recognized phenomenon⁹.

This study suggests that the sensitivity and specificity of serial leucocyte counts for acute appendicitis fulfil the criteria³⁴ for a diagnostic test (sensitivity >80 per cent and specificity >90 per cent). The value of serial CRP measurements in this series is not as great as that of serial WCCs, and appears to offer no advantage over that method.

The diagnosis of acute appendicitis is primarily clinical and should be made on clinical symptoms and signs. However, some patients have equivocal physical findings and may be admitted for a period of observation. We suggest that these patients could also have serial total WCCs taken as an aid to diagnosis. If this protocol had been applied to the patients in this study, 11 of 12 unnecessary appendicectomies would have been avoided. We do not have data on patients who were admitted, observed and not operated on, but the clinical course showed that operation was not necessary in these patients. We suggest that, on the basis of these results, a prospective randomized trial to evaluate the use of serial total WCCs in the diagnosis of acute appendicitis would be justified.

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Influence of 5-fluorouracil and folinic acid on colonic healing: an experimental study in the rat

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Male Wistar rats were subjected to colonic resection and randomized to one of four groups: control group (intraperitoneal NaCl, intravenous NaCl); 5-fluorouracil (5-FU) group (intraperitoneal 5-FU, intravenous NaCl); folinic acid group (intraperitoneal NaCl, intravenous folinic acid); and 5-FU-folinic acid group (intraperitoneal 5-FU, intravenous folinic acid). Treatment was started immediately after surgery and continued until the animals were killed at 3 or 7 days. Anastomotic complications (abscesses or dehiscence) occurred in four of 33 animals in the control group, 12 of 36 in the 5-FU group, one of 32 in the folinic acid group and nine of 36 in the 5-FU-folinic acid group. Anastomotic and skin breaking strength did not differ between groups on day 3 but by day 7 were significantly reduced in the 5-FU group. In rats given 5-FU-folinic acid, breaking strength was also reduced, but less so than in the 5-FU group. Breaking strength in animals receiving folinic acid was similar to that in the control group. In this model colonic healing was impaired after intraperitoneal 5-FU administration, but when folinic acid was added no further deterioration occurred.

High recurrence rates after curative resection for colorectal cancer have prompted investigations of chemotherapy as an adjunct to surgery; 5-fluorouracil (5-FU) has been widely used, but results after systemic administration have been disappointing¹, except in combination with levamisole². Findings after administration of intraperitoneal 5-FU have also been encouraging³. Alternatively, high hepatic⁴ and local concentrations can be obtained after intraperitoneal 5-FU infusion. In the treatment of metastatic disease, 5-FU combined with folinic acid is superior to 5-FU alone⁵. For these reasons, intraperitoneal 5-FU modulated by folinic acid should be tested as an adjuvant therapy. Wound healing was impaired by 5-FU in most⁶⁻⁸ but not all⁹ previous studies. It is not known how the negative effect of 5-FU on wound healing is altered when folinic acid is added. This question is important because experimental data have indicated that the efficiency of adjuvant therapy is inversely proportional to the time interval between surgery and therapy¹⁰.

The aim of this study was to assess how intraperitoneal 5-FU with or without the addition of folinic acid affects wound healing in the early period after surgery.

Materials and methods

A group of 137 male Wistar rats of median weight 268 (range 240-302) g (Møllegaard, Skensved, Denmark) was weighed daily and fed a standard laboratory diet and water *ad libitum*. The study was approved by the ethics committee of southern Sweden. The animals were anaesthetized with intraperitoneal fentanyl:midazolam:sterile water (1:1:2) 3.3 ml kg⁻¹. The right femoral vein was exposed and cannulated with a polyethylene catheter (Clay Adams PE50; Becton-Dickinson, New Jersey, USA), which was tunnelled subcutaneously to the neck. A 1-cm left colonic segment, 2 cm above the peritoneal reflection, was resected through a 3-cm midline incision. An end-to-end anastomosis was constructed with nine interrupted inverting sutures (Surgilene 7/0; Davis and Geck, New York, USA). The abdominal muscle layer and skin incision was closed with a running suture (Ti-Cron 5/0; Davis and Geck).

Experiment 1

After surgery the animals were randomized to: control group (intraperitoneal NaCl, intravenous NaCl); 5-FU group (intraperitoneal 5-FU, intravenous NaCl); folinic acid group (intraperitoneal NaCl,

intravenous folinic acid); and 5-FU-folinic acid group (intraperitoneal 5-FU, intravenous folinic acid). 5-FU (Hoffmann-La Roche, Basel, Switzerland) 5 mg ml⁻¹ in 0.9 per cent NaCl was given as an intraperitoneal injection at a daily dose of 20 mg kg⁻¹ and folinic acid (Cyanamid Nordiska, Sundbyberg, Sweden) 5 mg ml⁻¹ in sterile water 15-30 min later as an intravenous bolus injection at a dose of 2 mg kg⁻¹. NaCl was given intraperitoneally or intravenously in corresponding volumes. After the intravenous injection the catheter was heparinized (5000 units heparin per 100 ml NaCl). Treatment was started immediately after operation and continued until death in a carbon dioxide chamber on the third or seventh day after surgery.

Experiment 2

The second experiment was identical to the first with two exceptions: the folinic acid dose was 10 mg kg⁻¹ day⁻¹ and all animals were killed on day 7. The number of animals in each group is shown in Table 1.

In both experiments, blood was sampled before surgery and at death for analyses of haemoglobin, white blood cell (WBC) count and serum albumin. The abdomen was explored by an observer, blind to the treatment arm of the study, for anastomotic complications (abscesses and dehiscence). Affected animals were excluded from further statistical evaluation, but calculations including all animals were also performed with similar results (data not shown). The entire anastomotic segment was placed in a tensiometer with the anastomosis in the centre of the gap. The tensiometer provided an increasing force of 0.03-0.05 N s⁻¹. Anastomotic breaking strength was determined with the sutures left in place. After removal of the running suture, two 5 × 25 mm skin flaps were prepared from the area containing the abdominal skin incision. Skin wound breaking strength was similarly tested and the mean of the two determinations calculated.

Before placement of the bowel in the tensiometer, two sutures were placed 5 mm from each side of the anastomosis. After anastomotic breaking strength testing, the colon was divided at the sutures. The resulting 10-mm segment was cut at the mesenteric and antimesenteric sides, thereby obtaining two standardized anastomotic biopsies. Finally, all sutures were removed under a microscope. One part was analysed for hydroxyproline content¹¹ as a marker of collagen, and the counterpart for myeloperoxidase activity¹² as a marker of neutrophils¹³.

Statistical methods

Differences between treatment and control group means were evaluated using one-way analysis of variance and Duncan's multiple range test¹⁴ when indicated. Differences between proportions were assessed with the χ^2 test.

Table 1 Number of rats with complications

Group	n	Experiment 1 (n = 96)		n	Experiment 2 (n = 41)	
		Wound rupture	Anastomotic complications*		Wound rupture	Anastomotic complications*
Control	24	1†	3	9	1	1
5-FU	24	1†	8	12	0	4
Folinic acid	24	0	1	8	0	0
5-FU–folinic acid	24	1	7	12	1	2

5-FU, 5-fluorouracil; *macroscopic abscesses or dehiscence; †lethal complication

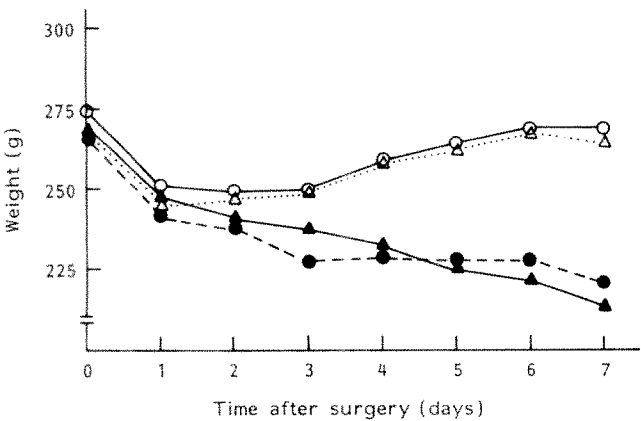


Figure 1 Weight development in experiment 1. ○, Control group; ●, 5-fluorouracil (5-FU) group; △, folinic acid group; ▲, 5-FU–folinic acid group

Table 2 White blood cell count at death

Group	Experiment 1		Experiment 2
	Day 3	Day 7	Day 7
Control	5.1(2.1)	4.4(2.2)	6.4(3.1)
5-FU	3.2(2.4)	4.6(1.6)	3.8(2.9)
Folinic acid	4.2(1.3)	6.2(3.2)	5.7(2.7)
5-FU–folinic acid	3.4(1.3)	2.8(1.1)	2.4(1.3)*

Values are mean(s.d.) expressed as 10^9 cells per litre. 5-FU, 5-fluorouracil. * $P < 0.01$ (5-FU–folinic acid group versus control, Duncan's multiple range test)

Results

Wound healing complications

Two of five animals with abdominal wound rupture died during the treatment period (Table 1). Anastomotic complications were more frequent in rats treated with 5-FU alone or in combination with folinic acid than in those not receiving 5-FU ($P = 0.01$). Folinic acid, either alone or combined with 5-FU, did not increase the number of anastomotic complications.

Weight and haematological analyses

Before operation there were no significant differences in weight, haemoglobin, WBC count or serum albumin levels between the groups in any experiment (data not shown). From the second day after operation, in both experiments, rats treated with 5-FU or 5-FU–folinic acid lost weight, whereas animals in the control and folinic acid groups regained weight (Figure 1). The haemoglobin level at death was not affected by treatment (data not shown), whereas animals receiving 5-FU–folinic acid had reduced WBC counts in experiment 2 (Table 2). Serum albumin levels were reduced after 5-FU and 5-FU–folinic acid treatment in experiment 2 (Table 3).

Table 3 Serum albumin determinations at death

Group	Experiment 1		Experiment 2
	Day 3	Day 7	Day 7
Control	49(15)	48(9)	45(12)
5-FU	41(13)	40(18)	31(7)*
Folinic acid	47(16)	49(11)	38(7)
5-FU–folinic acid	42(14)	44(12)	28(9)*

Values are mean(s.d.) expressed in $g\ l^{-1}$. 5-FU, 5-fluorouracil. * $P < 0.01$ (5-FU and 5-FU–folinic acid groups versus control, Duncan's multiple range test)

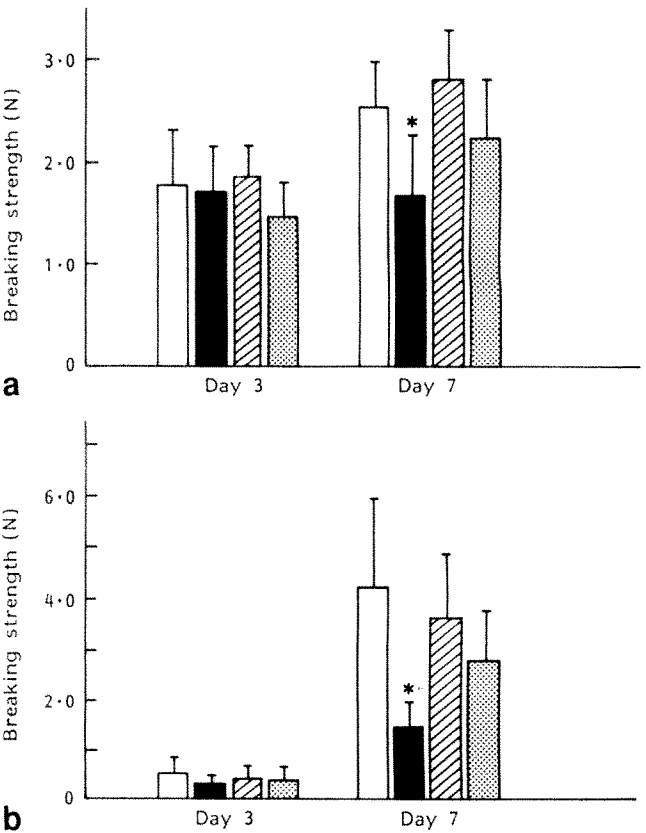


Figure 2 Mean(s.d.) a anastomotic and b skin breaking strength in experiment 1. □, Control group; ■, 5-fluorouracil (5-FU) group; ▨, folinic acid group; ▤, 5-FU–folinic acid group. * $P < 0.01$ (5-FU group versus control, Duncan's multiple range test)

Breaking strength

Anastomotic and skin breaking strengths did not differ between groups on day 3. By day 7, in both experiments, the 5-FU group had weaker anastomoses (both $P < 0.01$) and skin wounds ($P < 0.01$ and $P < 0.05$) compared with controls. Anastomotic ($P < 0.01$) and skin ($P < 0.05$) breaking strengths

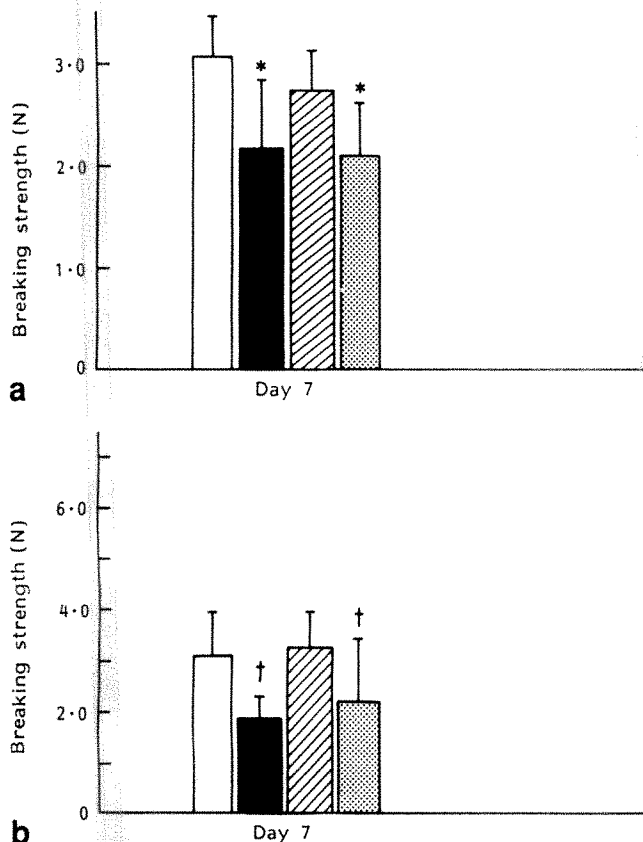


Figure 3 Mean(s.d.) **a** anastomotic and **b** skin breaking strength in experiment 2. □, Control group; ■, 5-fluorouracil (5-FU) group; ▨, folinic acid group; ▤, 5-FU-folinic acid group. * $P < 0.01$; † $P < 0.05$ (respective groups versus control, Duncan's multiple range test)

Table 4 Hydroxyproline and myeloperoxidase determinations

Group	Hydroxyproline content (μg per biopsy)		Myeloperoxidase activity (units per biopsy)	
	Day 3	Day 7	Day 3	Day 7
Experiment 1				
Control	185(66)	215(117)	0.14(0.08)	0.07(0.04)
5-FU	135(32)†	100(29)†	0.16(0.14)	0.11(0.08)
Folinic acid	202(51)	195(49)	0.24(0.11)	0.29(0.16)*
5-FU-folinic acid	146(33)	125(16)†	0.18(0.07)	0.31(0.10)*
Experiment 2				
Control	—	217(95)	—	0.12(0.13)
5-FU	—	177(46)	—	0.20(0.19)
Folinic acid	—	239(53)	—	0.15(0.07)
5-FU-folinic acid	—	172(73)	—	0.13(0.10)

Values are mean(s.d.). 5-FU, 5-fluorouracil. * $P < 0.01$; † $P < 0.05$ (respective groups versus control, Duncan's multiple range test)

were also reduced after 5-FU-folinic acid treatment in experiment 2 (Figures 2 and 3).

Hydroxyproline and myeloperoxidase

In experiment 1, anastomotic hydroxyproline content was reduced at day 3 in rats receiving 5-FU and at day 7 in the 5-FU and 5-FU-folinic acid groups ($P < 0.05$). In experiment 2, hydroxyproline content tended to be lower in the 5-FU and 5-FU-folinic acid groups (P not significant). Animals treated with the lower folinic acid dose had raised myeloperoxidase activity in the anastomotic biopsy (Table 4).

Discussion

This study was designed to resemble an adjuvant course where 5-FU is given intraperitoneally to obtain high hepatic and peritoneal concentrations and folinic acid intravenously after 5-FU to achieve schedule-dependent synergism¹⁵. Evaluation of folinic acid potentiation of the effect of 5-FU on wound healing should be performed at a biologically active 5-FU dose. In a pilot study, daily doses of 15, 17.5, 20 and 22.5 mg kg^{-1} for 7 days were tested in groups of four animals subjected to colonic resection. The highest dose caused death, whereas the two lower doses had no apparent influence on the postoperative course. A dose of 20 mg kg^{-1} caused a moderate weight loss and leucopenia and was therefore chosen for this study. The human equivalent¹⁶ is approximately 500 $\text{mg m}^{-2} \text{day}^{-1}$, which is a common dose in adjuvant intraportal trials³. Two dose levels of folinic acid were tested, corresponding to 80 and 400 mg m^{-2} in humans on a relative weight basis.

In the present study, 5-FU negatively influenced wound healing as judged by anastomotic complications and reductions in breaking strength. The negative effect was not increased when folinic acid was combined with 5-FU. When folinic acid at a dose of 2 $\text{mg kg}^{-1} \text{day}^{-1}$ was added to 5-FU, breaking strength in the anastomosis and skin was actually higher than after 5-FU alone, and not significantly different from that of controls. When interpreting results of experimental studies, differences between the model and the clinical situation should always be kept in mind (e.g. the presence of a primary tumour, species differences). Nevertheless, the present results indicate that 5-FU has a deleterious effect on wound healing that is not further increased when folinic acid at the dose range tested is added to 5-FU in adjuvant therapy.

The conflicting results in previous studies concerning the effect of 5-FU on wound healing are likely to be due to variations in cumulative 5-FU dose and experimental design⁶⁻⁹. A longer time interval between treatment interruption and death might reduce the differences between treatment and control groups owing to rapid restoration of wound healing. Therefore, the present animals were killed directly after the treatment period. Several rats developed anastomotic abscesses or dehiscence which might have distorted the biochemical and breaking strength determinations. These animals were excluded from further evaluation so as to study only the influence of chemotherapy.

With the sutures left in place, anastomotic breaking strength determinations on day 3 represent mainly suture holding capacity, whereas newly formed tissue in the wound gap contributes to the strength on day 7. On day 3, anastomotic and skin wound strengths did not differ between groups. On day 7 in the 5-FU group both were reduced compared with controls. Anastomotic hydroxyproline content was reduced on days 3 and 7 in 5-FU treated rats, irrespective of folinic acid addition, to 50–80 per cent of control levels. This might be due to impaired fibroplasia or increased lysis of collagen, or both. Leucocytes stimulate fibroplasia but also participate in collagen degradation. Anastomotic myeloperoxidase activity as a marker of leucocyte accumulation was determined in the hope of finding an explanation for altered wound healing. However, myeloperoxidase activity was not clearly related to measurements of anastomotic healing.

The 5-FU concentration in the present study was higher than in clinical trials¹⁷; the defective anastomotic healing could not be caused by a locally high concentration because skin healing was impaired to the same extent. 5-FU-treated rats were malnourished after operation as judged by their weight and serum albumin levels. However, malnutrition lasting for just 1 week has not affected wound healing in previous studies¹⁸. Further investigations are required to clarify the reason for deficient wound healing after 5-FU administration.

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Decreased sensitivity of muscarinic but not 5-hydroxytryptamine receptors of the internal anal sphincter in neurogenic faecal incontinence

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Pharmacological studies have demonstrated decreased sensitivity of the internal anal sphincter to the contractile actions of noradrenaline in patients with neurogenic faecal incontinence¹. Whether in this condition there is also an abnormality of the other important receptors involved in the innervation of the internal anal sphincter is not known. The responsiveness of the internal anal sphincter to carbachol and to 5-hydroxytryptamine (5-HT) in neurogenic incontinence was examined. 5-HT is believed to be an important neural mediator in the myenteric plexus²⁻⁴ and known to be present in neurones that innervate the internal anal sphincter⁵.

Responses to carbachol and 5-HT were compared between muscle strips from patients with demonstrated neurogenic incontinence and control patients undergoing operation for low carcinoma of the rectum, to determine whether there were any differences indicative of altered cholinergic and serotonergic control of this tissue.

Patients and methods

Patients

Seven women undergoing postanal repair for incontinence to solid stool were studied. Their mean age was 55 (range 26-87) years. Three of these patients also suffered from urinary incontinence. All the women were parous and four had required forceps delivery. The mean number of vaginal deliveries for all seven women was three (range one to six). None of the patients reported abnormal bowel function before childbirth and there was no evidence of other neurological disease.

Controls

Ten patients undergoing abdominoperineal resection for low rectal carcinoma were studied as controls. There were six women and four men, of mean age 57 (range 44-82) years. None of the control patients had a history of faecal incontinence or altered bowel habit before the development of the rectal tumour.

The study was approved by the City and Hackney District Ethical Committee and all subjects gave informed consent.

Previous studies of the internal anal sphincter in patients with neurogenic faecal incontinence have indicated an abnormality of the adrenergic innervation, but little is known about the responsiveness of other receptors in the internal anal sphincter in this condition. In this study the in vitro sensitivity to carbachol and 5-hydroxytryptamine (5-HT) of muscle strips from patients with neurogenic incontinence (n = 6 and n = 7) and from control patients (n = 9 and n = 10) was examined. Preparations of internal anal sphincter from patients with incontinence were less sensitive to the relaxant actions of carbachol than preparations from the control group. The pD₂ value for carbachol (i.e. the negative logarithm of the concentration for half-maximal response) was significantly greater in the controls than in the incontinent group (mean(s.e.m.) 6.03(0.15) versus 5.43(0.24), P < 0.05). There was no significant difference in the contractile responses to 5-HT, which had pD₂ values of 6.93(0.13) and 6.63(0.27) for the control and incontinent groups respectively. The unaffected state of the 5-HT receptor and the subsensitivity of the muscarinic receptor are discussed in relation to intrinsic neural control of the internal anal sphincter in neurogenic faecal incontinence.

Methods

Anorectal physiology. Anorectal physiology was performed before operation in all incontinent subjects to confirm a neuropathic cause for the incontinence. Maximum resting anal pressure and maximum voluntary contraction pressures were measured using a closed water-filled system with a 4-mm diameter microballoon connected through a 2-mm non-compliant plastic catheter to a pressure transducer (Medex MX-848, Rossendale, UK) and a chart recorder (Devices MX4-73, Welwyn Garden City, UK). Pudendal nerve terminal motor latencies and single-fibre electromyography (EMG) of the external anal sphincter were performed using methods described previously^{6,7}. Concentric needle EMG was performed to assess the structural integrity of the external anal sphincter. It was not felt justified to carry out these tests in the control group.

Tissues studied. Transverse strips of the internal anal sphincter 10 mm long and 3 mm wide were taken during the intersphincteric dissection of postanal repair. In controls, the equivalent most distal strip of the internal sphincter was taken from the resected abdominoperineal specimen. The strips were placed into modified Krebs' solution in the operating theatre and transferred into organ baths containing Krebs' solution gassed with 95 per cent oxygen and 5 per cent carbon dioxide.

In vitro experiments. Between two and four muscle strips were dissected from the tissue under a dissecting microscope and each was suspended in a 5-ml organ bath containing modified Krebs' solution (NaCl 133 mmol l⁻¹, KCl 4.7 mmol l⁻¹, MgSO₄ 0.6 mmol l⁻¹, NaHCO₃ 16.3 mmol l⁻¹, CaCl₂ 2.5 mmol l⁻¹ and glucose 7.7 mmol l⁻¹). Porcine insulin (50 units l⁻¹ at pH 3.0) was added to a concentration of 25 milliunits l⁻¹, and thiamine pyrophosphate (cocarboxylase) (50 nmol l⁻¹), bovine serum albumin (0.1 per cent) and the bacterial and non-specific peptidase inhibitor bacitracin (1500 units l⁻¹) were also added to the Krebs' solution. The organ bath was warmed to 37 ± 0.5°C and the Krebs' solution gassed with 95 per cent oxygen and 5 per cent carbon dioxide maintaining pH 7.3-7.4. Strips were allowed to equilibrate for 1 h before agonists were tested. Contractile and relaxant responses were recorded using force-displacement transducers (FTOC3; Grass Instruments, Quincy, Massachusetts, USA)

and displayed on an ink-writing oscillograph (Grass Instruments). A spring (spring constant 0.3 g cm^{-1}) was in series with the preparation and the transducers so that the activity of the muscle strip was recorded under auxotonic conditions.

Carbachol. Carbachol was added to the organ bath to produce final graded concentrations ranging from 10^{-8} to $10^{-3} \text{ mol l}^{-1}$. Atropine ($10^{-6} \text{ mol l}^{-1}$) was added to the Krebs' solution and after the strips had been allowed to equilibrate in this solution for 20 min the responses to carbachol were again determined. Carbachol studies were performed in six patients and nine controls.

5-hydroxytryptamine. 5-HT was added to the organ bath in the concentration range 3×10^{-9} – $10^{-4} \text{ mol l}^{-1}$.

Analysis of results

To obtain concentration–response curves, single doses of agonist were added to the organ baths and after the maximum response had been recorded the agonist was washed out with Krebs' solution. At least 10 min was allowed before adding the next dose of the agonist. The responses for each preparation were expressed as a percentage of the maximum response, and using probit transformations the sigmoidal log concentration–response curve was converted to a straight line. From the linear regression of the probit values, the logarithm of the concentration required to produce 1, 5, 10, 20, 35, 50, 65, 80, 90, 95 and 99 per cent maximum responses was calculated^{8,9}. The curves represent the mean of the log concentrations for all the preparations for each of these percentage points. This method provides information over the 1–99 per cent part of the concentration–response curves and avoids bias towards a lower slope¹⁰. From the curves, the negative logarithm of the concentration required to produce 50 per cent of the maximum response (pD_2) was calculated. For each group of preparations the mean (s.e.m.) pD_2 was determined.

Because of variation in the size of the muscle strips the overall

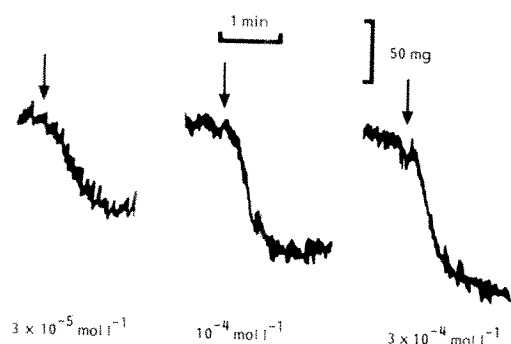


Figure 1 Polygraph recording of relaxation with addition of increasing concentrations of carbachol

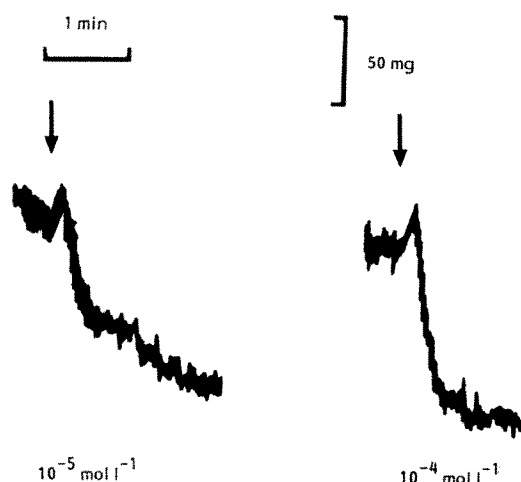


Figure 2 Polygraph recording of response to carbachol showing an initial small contraction followed by a larger relaxation. This type of response was seen in muscle strips from five controls and three incontinent patients

absolute magnitude of contractions was not compared between muscle strips. Comparison was made between concentrations required to produce half-maximal responses, thus giving an indication of possible changes in sensitivity.

Results

Anorectal physiology

All the patients were found to have neuropathic damage of the pelvic floor. The mean maximum resting anal pressure was reduced at 34 (range 5–60) cmH_2O (normal in this laboratory is 40–100 cmH_2O). The mean maximum voluntary contraction pressure was 12 (range 0–30) cmH_2O compared with a normal range of 40–160 cmH_2O . Anal pressures were therefore below or at the lower limit of normal. The pudendal nerve terminal motor latency was prolonged in all patients (mean 2.54 (range 2.3–2.9) ms, normal⁷ ≤ 2.2 ms). The single-fibre density of the external anal sphincter, a measure of reinnervation¹¹, was also raised in all patients (mean 2.2 (range 1.8–2.7), normal⁶ ≤ 1.7). Concentric needle EMG did not reveal any defects in the external anal sphincter; in particular the anterior sphincter was intact. These patients were selected for postanal repair operation on the basis of these physiology results and represent a group of incontinent patients with neurogenic incontinence.

Carbachol

The predominant response to carbachol in strips from both controls and incontinent patients was relaxation (Figure 1), but in five of the nine controls and in three of the six incontinent patients there was a small initial contraction (Figure 2). The addition of atropine ($10^{-6} \text{ mol l}^{-1}$) blocked both the initial contraction and the relaxation. The pD_2 value in the control group was 6.03(0.15) and in the incontinent group 5.43(0.24) ($P < 0.05$, unpaired t test). The concentration–response curves also had different slopes and diverged significantly above the 50 per cent level (Figure 3). The maximum response was produced using a mean concentration of $1.67 \times 10^{-5} \text{ mol l}^{-1}$ carbachol in controls and with $2.3 \times 10^{-4} \text{ mol l}^{-1}$ in incontinent patients; these values differed significantly ($P < 0.05$). There was no significant difference in pD_2 between female and male controls (5.96(0.12) versus 6.06(0.26)).

5-hydroxytryptamine

5-HT produced contractions in all strips (Figure 4) but in four of the ten controls the response was biphasic with a secondary

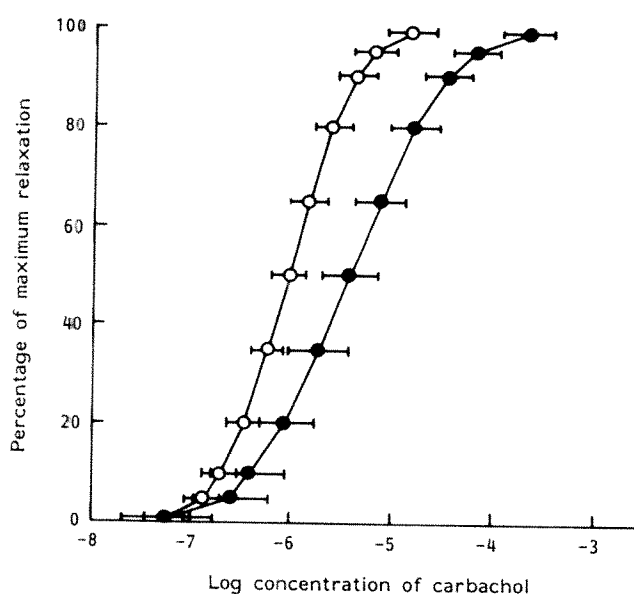


Figure 3 Concentration–response curves to carbachol. Values are mean (s.e.m.). ○, Controls ($n = 9$); ●, incontinent patients ($n = 6$). There was a significant difference in the curves from the half-maximal response level upwards

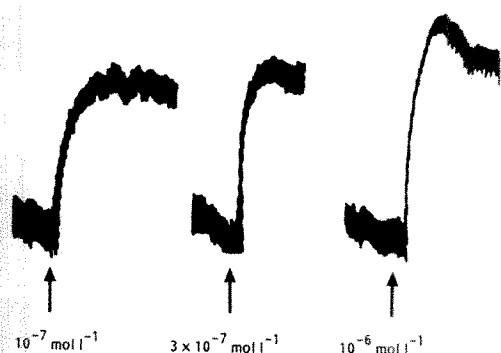


Figure 4 Polygraph recording of contractions with addition of increasing concentrations of 5-hydroxytryptamine

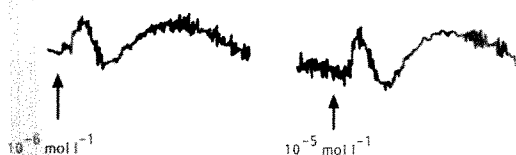


Figure 5 Polygraph recording of response to 5-hydroxytryptamine showing a biphasic response

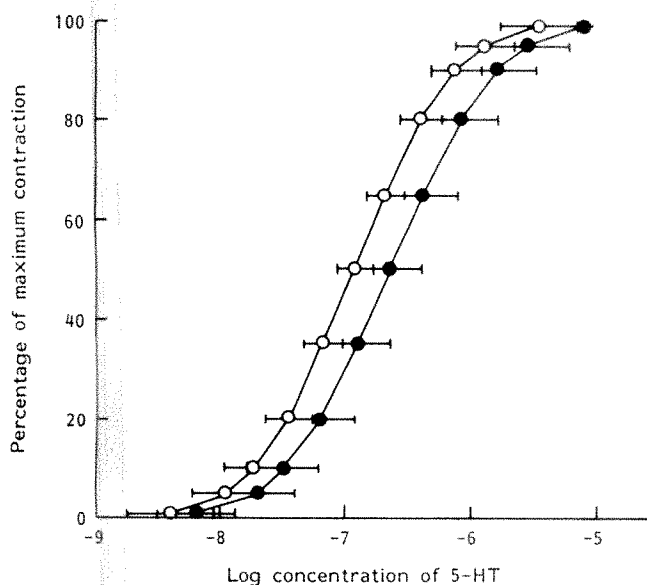


Figure 6 Concentration-response curves to 5-hydroxytryptamine (5-HT). Values are mean (s.e.m.). ○, Controls (n = 10); ●, incontinent patients (n = 7). There was no significant difference between the curves

slower contraction (Figure 5). This biphasic contraction was also seen in a muscle strip from one incontinent patient.

The pD_2 values were not significantly different between the control group and the incontinent group (6.93(0.13) versus 6.63(0.27), $P > 0.05$) and the concentration-response curves were also not significantly different at any concentration (Figure 6). There was no significant difference between pD_2 of female and male controls (7.02(0.19) versus 6.82(0.19), $P > 0.05$).

Discussion

This study has shown that in neurogenic faecal incontinence there is a decreased sensitivity to carbachol but no change in sensitivity to 5-HT. Although a change in sensitivity to

carbachol is indicative of an altered cholinergic control mechanism in patients with incontinence, this study has not identified where this dysfunction lies. However, the 5-HT studies show that there are no changes in the sensitivity of 5-HT receptors and suggest that this component of the intrinsic neural regulation is intact. The normal response to 5-HT also demonstrates that the smooth muscle cells in incontinent patients are capable of a normal contractile response.

Previous studies have shown that stimulation of the parasympathetic innervation produces relaxation of the internal anal sphincter, probably through the action of acetylcholine on muscarinic receptors¹². Acetylcholine has been shown to cause both relaxation and contraction of the internal anal sphincter in *in vitro* studies¹³. A biphasic response has also been observed although the contractile response is always small in comparison with the relaxation⁵, and both effects are believed to be mediated by muscarinic receptors. The present study confirms these findings.

The reason for the biphasic response seen with 5-HT in some muscle strips is not known but it may be caused by stimulation of different 5-HT receptor types that remain to be classified.

Previous reports of decreased sensitivity to noradrenaline and the present finding of an altered cholinergic receptor sensitivity could be explained by long-standing damage to the autonomic innervation of the sphincter. Following experimental denervation, the acute response is often a supersensitivity caused by the loss of active uptake sites in the nerve terminals^{14,15}. However, in these animal studies only relatively acute denervation was studied, and the long-term effects of denervation, more relevant to patients with neurogenic faecal incontinence, have not been studied. Subsensitivity of cholinergic receptors has been reported following sympathetic denervation of cat sweat glands¹⁶.

The present results fit the hypothesis that in patients with neurogenic faecal incontinence there is not only damage to the somatic innervation of the striated pelvic floor muscles, but there is also an abnormality of extrinsic sympathetic and intrinsic or extrinsic cholinergic innervation of the internal anal sphincter. The cause of an autonomic neuropathy is unclear, but our knowledge of the anatomy of the autonomic innervation of the internal anal sphincter is not complete and it is possible that the process causing injury to the pudendal nerve also damages the autonomic supply. Alternatively, the changes described may be part of a primary disorder of the sphincter mechanism. In conclusion, this study has shown a subsensitivity of cholinergic receptors suggesting possible autonomic denervation of the internal anal sphincter in patients with neurogenic faecal incontinence.

Acknowledgements

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Screening for colorectal carcinoma: an analysis of the sensitivity of Haemoccult

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The sensitivity of Haemoccult for asymptomatic colorectal carcinoma has been estimated in a large randomized controlled trial of mass population screening, with a minimum follow-up of 2 years. A total of 111 cancers were diagnosed in those who completed the screening tests; of these, 36 appear to have been missed by Haemoccult and 75 were detected by the test, giving an overall sensitivity of 67.6 per cent. Haemoccult was shown to be significantly more sensitive for carcinoma of the sigmoid and descending colon than for rectal or right-sided cancers (81 versus 45 and 47 per cent, respectively). The sensitivity was higher when tests were completed over 6 rather than 3 days (74 versus 65 per cent), but this difference was not statistically significant. There was no evidence for a detrimental effect on tumour stage of a false-negative Haemoccult test; indeed, a higher proportion of the interval cancers were Dukes' A tumours than cancers in the control group.

Faecal occult blood screening for asymptomatic colorectal carcinoma is currently the subject of randomized controlled trials in Europe and the USA. Although a mortality advantage has yet to be proved, interim results from these trials are encouraging, with a significantly higher proportion of the screen-detected cancers being localized to the bowel in comparison with control populations¹⁻⁴.

The faecal occult blood test used in these studies was Haemoccult (Roehm, Darmstadt, Germany), a slide preparation of guaiac gum, which relies on the peroxidase activity of haematin to catalyse the phenolic oxidation of the substrate. All trial reports have emphasized that one of the major limitations of Haemoccult as a screening agent is its limited sensitivity for asymptomatic carcinomas.

The sensitivity has generally been calculated from the interval cancer rate, that is cancers that are diagnosed in the interval between a negative test and a rescreen, typically at 2 years, it being assumed that such cancers were missed at the time of screening. However, no detailed analysis of interval cancer rate has been made; in particular there has been no allowance for the erroneous effect on sensitivity calculations introduced by the follow-up period necessary after screening. In an ongoing screening programme, screen-detected cancers continue to be diagnosed whereas the interval cancers may take as long as 2 years to emerge (if screening is performed at 2-year intervals).

The aim of this analysis was, therefore, to estimate the overall sensitivity of Haemoccult for asymptomatic colorectal carcinoma in a programme of screening and rescreening at 2-year intervals with a minimum follow-up period of 2 years for all those who completed the tests. The study also examined the variation in sensitivity according to tumour site and the possible adverse effect of reassurance on cancer stage at the time of presentation in those with false-negative tests. The sensitivity of the test when performed over 3 or 6 days has also been compared.

Patients and methods

A minimum follow-up of 2 years is available on 111 146 asymptomatic subjects (50-74 years of age) recruited into the Nottingham Colorectal Cancer Screening Study. These subjects were randomly allocated to a test or control group.

The test group were sent Haemoccult tests to be performed over 3

or 6 days with a letter of invitation from their general practitioners. Those with positive results were further investigated by colonoscopy or double-contrast barium enema and flexible sigmoidoscopy⁵.

Of the 52 732 people offered Haemoccult, 27 027 (51.3 per cent) completed the tests. A total of 2840 people offered Feca EIA (Labsystems, Helsinki, Finland)^{5,6} have been excluded from this analysis. Subjects at the initial screen have lately been further randomized to complete 3 or 6 days of tests⁷.

Subjects who participated in the initial screen were rescreened at 2-year intervals; at the time of analysis 8219 had been rescreened once and 2972 twice. All have been followed up for 2 years. Interval cancers are defined as those presenting in the interval between a negative test and a rescreen or within 2 years of a final screen.

Subjects in the test group who refused Haemoccult and those with negative Haemoccult tests have been monitored for the development of colorectal carcinoma by scrutiny of the pathology records of the catchment area hospitals and by information supplied by the Trent Cancer Registry and the National Health Service Central Registry.

Haemoccult tests were interpreted in this department without rehydration. Subjects with positive results were assessed in a designated clinic and underwent colonoscopy or double-contrast barium enema examination with flexible sigmoidoscopy.

Dukes' classification was used, with the addition of a class 'D' for patients with distant metastases.

Statistical comparisons were made using the χ^2 test, with Yates' correction when required.

Results

Sensitivity for asymptomatic colorectal carcinoma

At the initial screen 586 (2.2 per cent) of those completing Haemoccult had positive tests; 141 (1.7 per cent) were positive at the first rescreen, and ten (0.3 per cent) at the second rescreen.

Sixty-three cancers were diagnosed at the initial screen, 11 at the first rescreen and one at the second rescreen. In all, 75 cancers were diagnosed in 38 218 screening episodes (27 328 over 3 days and 10 890 over 6 days) in 27 027 subjects. Among those with negative Haemoccult tests, 36 interval cancers have been diagnosed after the development of symptoms.

Thus, a total of 111 cancers have been diagnosed in the screened group (Table 1); 36 appear to have been missed by Haemoccult and 75 detected by the test, giving an overall sensitivity for asymptomatic colorectal cancer of 67.6 per cent.

Over the study period 90 cancers were diagnosed in the non-responding group (those who refused Haemoccult tests) and 152 in the control group.

Site-dependent sensitivity

The anatomical site of screen-detected and interval cancers is shown in Table 1. The sensitivity of Haemoccult was greatest for left colonic carcinomas (sigmoid and descending colon) where 81 per cent of the tumours were detected (Table 2). This was significantly greater than the 45 per cent sensitivity achieved for rectal cancers ($\chi^2 = 10.43$, 1 d.f., $P = 0.001$) and the 47 per cent sensitivity seen for carcinoma of the ascending colon or caecum (Yates' $\chi^2 = 5.97$, 1 d.f., $P = 0.01$). There was no significant difference when compared with transverse colon cancers (Yates' $\chi^2 = 1.22$, 1 d.f., $P = 0.27$).

Sensitivity of Haemoccult over 3 or 6 days (Table 3)

Of the 27 328 completed 3-day Haemoccult tests, 522

(1.9 per cent) were positive and 26 806 negative. Investigation of those with positive reactions revealed 50 colorectal carcinomas; a further 27 interval cancers have been diagnosed following the investigation of symptoms. Thus, of the 77 cancers diagnosed in those who completed 3-day Haemoccult, 27 (35 per cent) appear to have been missed by the test, giving a sensitivity of 65 per cent for asymptomatic carcinoma.

Similarly, there were 10 890 completed 6-day Haemoccult tests, 215 (2.0 per cent) of which were positive. Among those with positive tests, 25 cancers were diagnosed; a further nine interval cancers appeared in the 2-year period after a negative test. Thus, of the 34 cancers diagnosed in those who completed 6-day Haemoccult, nine (26 per cent) were missed at screening, giving a sensitivity of 74 per cent for asymptomatic cancer.

The difference in sensitivity for 3-day and 6-day testing is not statistically significant ($\chi^2 = 0.79$, 1 d.f., $P = 0.4$).

Table 1 Site of screen-detected and interval cancers

Site	Screen-detected cancer	Interval cancer	Total
Rectum (< 10 cm)	10	12	22
Sigmoid and descending colon	52	12	64
Transverse colon and flexures	6	4	10
Ascending colon and caecum	7	8	15
Total	75	36	111

Table 2 Site-dependent sensitivity of Haemoccult

Site	Interval cancer rate	Sensitivity (%)
Rectum (< 10 cm)	12 of 22 (55)	45
Sigmoid and descending colon	12 of 64 (19)	81
Transverse colon and flexures	4 of 10 (40)	60
Ascending colon and caecum	8 of 15 (53)	47
Total	36 of 111 (32)	68

Values in parentheses are percentages

Table 3 Two-year follow-up of patients completing 3-day or 6-day Haemoccult tests

	Haemoccult test	
	3-day	6-day
Completed tests	27 328	10 890
Positive	522* (1.9)	215† (2.0)
Screen-detected cancers	50	25
Interval cancers	27	9
Interval rate	27 of 77 (35)	9 of 34 (26)
Sensitivity (%)	65	74

Values in parentheses are percentages. *Includes rescreens; †initial screen only

Table 4 Cancer stage by study group

Dukes' classification	Screen-detected cancer	Interval cancer	Non-responders*	Control group
A	40 (53)	11 (31)	15 (17)	15 (10)
B	17 (23)	7 (19)	31 (34)	46 (30)
C	14 (19)	10 (28)	16 (18)	48 (32)
'D'	4 (5)	8 (22)	28 (31)	40 (26)
Not known	0 (0)	0 (0)	0 (0)	3 (2)
Total	75	36	90	152

Values in parentheses are percentages. *Those who refused the Haemoccult test

Effect of a false-negative Haemoccult test on cancer stage

Results with regard to Dukes' classification are shown in Table 4. The initial concern that a false-negative Haemoccult test would result in a high proportion of the interval cancers being advanced at the time of presentation (because of a 'reassurance' effect) was not borne out: there was an overall difference in the Dukes' distribution of the interval cancers in comparison with the non-screened control group ($\chi^2 = 10.40$, 3 d.f., $P = 0.01$), but this was due to a higher proportion of Dukes' A tumours in the interval group (31 versus 10 per cent in the control group; Yates' $\chi^2 = 6.14$, 1 d.f., $P = 0.01$). There was no significant difference between the two groups for other tumour classes ($\chi^2 = 0.9$, 2 d.f., $P = 0.6$).

Discussion

There are methodological problems in assessing the sensitivity of any mass screening procedure. Ideally the screening test should be compared with a 'gold standard' accepted as being the most sensitive means of detecting the condition in question. In the case of Haemoccult screening this would involve a comparison of the faecal occult blood test with colonoscopy, or double-contrast barium enema and flexible sigmoidoscopy. However, the vast number of people who would require such investigations makes this approach logistically impractical. The calculation of sensitivity has therefore been based on the rate of interval cancers as described.

Previous estimates of the interval cancer rates as a proportion of the total number of cancers in those who completed Haemoccult tests have permitted important comparisons of sensitivity between trials, but have failed to allow an adequate period of follow-up for the emergence of missed cancers among those with negative tests. Early results from the Danish trial⁸ of an interval cancer rate of 19.5 per cent were similar to those of 22 per cent reported from Nottingham³.

Using similar methods of analysis, Kewenter *et al.*¹ reported an overall interval cancer rate of 31.4 per cent from Göteborg (sensitivity for carcinoma 68.6 per cent) although this involved a variable period for rescreening of between 12 and 24 months

and the introduction of test card rehydration. The striking feature of that study is the low sensitivity of Haemoccult for cancer when test card rehydration was not used: of 18 cancers diagnosed in patients tested without rehydration, there were 14 interval cancers. These were assumed to have been missed by Haemoccult. It must be emphasized that this low sensitivity of 22 per cent is at odds with results of other screening trials. In the Minnesota study⁴, where rescreeing was at 12-month intervals, a sensitivity of 89.3 per cent was claimed for unrehydrated Haemoccult.

The variation in sensitivity according to tumour site has been reported previously from Nottingham and Funen^{2,3,9}. The reason for the poor sensitivity for rectal cancers is probably twofold. First, there may be uneven mixing of blood in the stool resulting in a sampling error; second, it has been proposed that the fresh blood commonly associated with low rectal cancers has an insufficient level of the haematin necessary to catalyse the reaction of phenolic oxidation upon which the Haemoccult test depends. The relative importance of these hypotheses remains unknown but unpublished data from this department have shown that if Haemoccult and an immunological test (not haematin dependent) are used in the same patients, the increased sensitivity for the immunological test is particularly marked for rectal cancers. This comparison was made using the same faecal sample to minimize sampling error; the results suggest that insufficient release of haematin is an important factor.

The possible reassurance offered by a false-negative test is of great concern to all involved in cancer screening programmes, but is especially pertinent for programmes that utilize a test of such limited sensitivity as Haemoccult. The influence of a false-negative test is difficult to ascertain with any degree of certainty but it is reassuring that a greater proportion of the interval cancers than those in the control group were Dukes' A. This may be partly explained by a selection bias favouring early-stage tumours among those individuals who accepted the invitation to complete the screening tests but it suggests that a false-negative test is unlikely to lead to undue delay in presentation of symptomatic cancer, in confirmation of an earlier report¹⁰ when a 2-year follow-up analysis was not made.

There is a suggestion that the yield of carcinoma tends to be greater when 6 days of Haemoccult tests are completed rather than the more usual 3 days, but previous reports have not shown a significant difference⁷. The present study is consistent with these earlier findings; once again the sensitivity difference was not statistically significant. The advantage of 6-day testing remains questionable, especially in view of the detrimental effect it has on compliance⁷.

Despite its limited sensitivity for carcinoma, Haemoccult is likely to remain the test of choice for mass screening in the foreseeable future because of its excellent specificity for neoplasia. Even though there may be a number of false-positive reactions resulting from dietary interference, specificity rates in

excess of 99 per cent can be achieved in the absence of test card rehydration^{2,3}. The test identifies a group of individuals, amounting to no more than 1–2 per cent of the population who are at particularly high risk of harbouring an asymptomatic carcinoma or adenoma. While an improvement in the sensitivity of faecal occult blood testing for cancer is desirable it must be achieved without an unacceptable loss in specificity.

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Local recurrence after anterior resection for rectal cancer using a double stapling technique

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Fifty-five patients of mean age 69 (range 41-96) years with rectal cancer (Dukes' A: B: C, 11: 24: 20) underwent anterior resection using a double stapling technique under the care of one consultant surgeon between 1983 and 1988. The mean distance of the anastomosis from the anal margin was 7.2 (range 4-13) cm. The clinical leak rate was 9 per cent (five patients). There were three postoperative deaths from pulmonary embolism, lower limb ischaemia and renal failure. On prospective follow-up, 35 patients had no evidence of local or systemic cancer a median of 32 (range 24-84) months after operation; seven have died from unrelated diseases and ten from metastatic cancer. Pelvic recurrence, in four patients at 9, 11, 12 and 50 months, has occurred only in association with widespread metastasis. These results suggest that the theoretical risks of an increase in the local recurrence rate of rectal cancer after resection using a double stapling technique are not substantiated.

The circular stapling device has been acknowledged as a significant advance in gastrointestinal surgery, particularly in colorectal anastomosis after low anterior resection¹⁻⁴. The original circular stapling technique¹ involves the insertion of a purse-string suture in the cut edge of the rectum or anal canal. The difficulty sometimes encountered with insertion of the purse-string and the size discrepancy between the rectum and colon often pose technical problems. In 1980 Knight and Griffen⁵ described a double stapling technique in which the rectum is cross-stapled with a linear stapling device before peranal introduction of the circular stapler. This method is said to overcome the problem of insertion of the purse-string on the rectal stump and also deals with any disparity in size between the rectum and colon⁵⁻⁹.

However, there is a theoretical risk of implantation of viable luminal cells at the transverse staple line. A further concern with the double stapling technique has been the risk of anastomotic failure at intersecting points where the staple lines cross. In experimental studies on dogs, Julian and Ravitch¹⁰ showed that anastomotic leakage was rare when a double stapling technique with intersecting staple lines was used for colorectal anastomosis. Despite this, the reported leak rate in clinical studies has been relatively high^{4,6}.

The aim of this study was to follow up all patients who had undergone anterior resection for rectal cancer under the care of one consultant using the double stapling technique. Local recurrence was particularly considered as a measure of outcome. The minimum follow-up was 2 years, the period during which 80-90 per cent of local recurrences will manifest after resection for colorectal cancer¹¹.

Patients and methods

Between 1983 and 1988, 55 patients with a histological diagnosis of adenocarcinoma were selected for anterior resection using the double stapling technique. There were 32 men and 23 women of mean age 69 (range 41-96) years. All operations were elective and the senior author (D.F.) performed or assisted in 51 of 55 operations (93 per cent). All patients had mechanical bowel preparation and were given prophylactic antibiotics on induction of anaesthesia.

Laparotomy was performed through a midline incision with the patient in the Lloyd-Davies position. After division of the inferior mesenteric vessels and mobilization of the sigmoid colon and rectum, the lateral ligaments were divided and ligated to allow clearance of the mesorectum¹². The rectum was carefully cleaned down to the muscle tube in preparation for anastomosis. Anastomosis was performed by a standard double stapling technique with the central rod of the circular stapler passing through the transverse staple line¹⁰. An important point in the technique is that, after mobilization, an angled bowel clamp is placed across the rectum, ideally 2-3 cm distal to the tumour, and the rectal stump irrigated with a cytotoxic solution. The rectum is then cross-stapled distal to the clamp using a TA55 linear stapler (Auto Suture, Ascot, UK) (Figure 1). The rectal 'doughnut' always transects the transverse staple line at two points on its circumference.

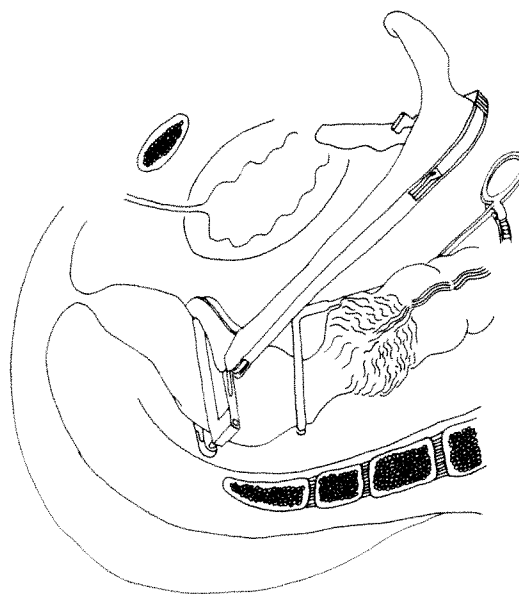


Figure 1 An angled bowel clamp (Hayes-Lowe) is placed across the rectum, ideally 2-3 cm distal to the tumour. The rectal stump is irrigated perianally with povidone-iodine, right up to the bowel clamp. The rectum is then cross-stapled below the clamp. In this series the TA55 linear stapler (4.8-mm staples) was used

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The anastomosis was routinely tested for leaks by intraoperative air insufflation with the pelvis filled with saline. Postoperative contrast studies to detect radiological leaks were not carried out unless clinically indicated. Patients were followed up at 3-month intervals for 1 year and 6-monthly thereafter.

Results

The mean level of the lower border of the tumour from the anal margin was 11 (range 7–18) cm. The mean anastomotic distance was 7.2 (range 4–13) cm. A covering transverse colostomy was fashioned in five patients; indications were an intraoperative leak in one patient and a low anastomosis in four (4 cm in two patients and 5 cm in two). In all patients the anastomotic rings ('doughnuts') were intact, although intraoperative air testing demonstrated one leak. This was repaired with interrupted sutures and a covering colostomy raised. There was one failure in cross-stapling when the surgeon omitted to fire the linear stapler. This necessitated insertion of a peranal purse-string suture¹³.

There were three postoperative deaths (mortality rate 5 per cent). One patient died at 6 days from pulmonary embolism, one at 6 days from bilateral leg gangrene and in one patient a postoperative leak developed; despite the creation of a colostomy the last patient died at 16 days from renal failure secondary to sepsis. The clinical leak rate was 9 per cent (five patients). All five underwent a second laparotomy with peritoneal lavage and a transverse colostomy; four recovered.

Other postoperative complications were urinary retention (two patients) and urinary infection (one), bleeding duodenal ulcer (one), bleeding from the anastomosis (one), small bowel obstruction (one), non-fatal pulmonary embolism (one) and a transient ischaemic attack (one).

Histological examination of the resected specimen confirmed adenocarcinoma in all cases. The tumour classification was Dukes' A in 11 patients, Dukes' B in 24 and Dukes' C in 20 (one patient also had liver metastases).

During follow-up three patients were noted to have an anastomotic stricture on digital examination. One was symptomatic and underwent successful dilatation under general anaesthesia.

Seven patients have died from unrelated diseases 3–36 months after anterior resection. Ten patients have died from metastatic cancer (two Dukes' B, eight Dukes' C), and in four of these pelvic recurrence was detected in association with disseminated metastatic cancer at 9, 11, 12 and 50 months after operation. Local recurrence has not been detected in the absence of distant metastasis.

Discussion

The safety and reliability of circular stapling instruments for colorectal anastomosis are now generally acknowledged. Advantages have been claimed for stapled compared with hand-sewn anastomoses in certain circumstances, particularly in low anterior resection for rectal cancer^{1–4}. However, all are agreed that the use of an instrument must not compromise the radicality of the operation^{1–4}.

A theoretical concern with the double stapling technique has been the possible increase in local recurrence rate. It has been postulated that this might result from luminal implantation of viable tumour cells during cross-stapling. Suture implantation of luminal tumour cells has been demonstrated in animals¹⁴. Furthermore, Phillips and Cook¹⁵ have shown that steel wire (or staples) has an adverse effect on local recurrence. If tumour implantation and an adverse effect of staples pose substantial risks, then anastomotic recurrence following the double stapling technique might well be a major problem. It is now generally accepted that 80–90 per cent of local recurrence will be manifest at 2 years after resection of rectal cancer¹¹. Recurrence rates of 8–55 per cent after either anterior resection or abdominoperineal excision of the rectum have been reported¹¹.

In the present series, with a minimum follow-up of 2 years, pelvic recurrence has been detected in four patients but only in association with disseminated disease. This is in contrast to a reported⁶ local recurrence rate of 16 per cent in 68 patients treated with the double stapling technique and followed up for 4–59 months.

In the current study a large proportion of the operations were performed or supervised by a single surgeon using a standardized technique. Recent reports have emphasized the large variation between individual surgeons in the incidence of local recurrence⁸.

We consider it essential in this technique to cross-clamp the lumen distal to the tumour before a thorough irrigation of the rectum with a cytotoxic solution (Figure 1). The most effective cytotoxic solutions are chlorhexidine–cetrimide and povidone–iodine, which rapidly kill exfoliated malignant cells¹⁶, although it may well be that peranal irrigation exerts its effect mainly by mechanical washout of exfoliated cells.

The clinical leak rate of 9 per cent in this series is within the range of reported rates (3.2–25 per cent) after anterior resection in which the EEA Stapler (US Surgical, Norwalk, Connecticut, USA) alone was used^{17–20}. However, a 9 per cent leak rate is undesirable and may partly reflect the learning curve of the operators. The authors of a number of series have reported that a double stapling technique for colorectal anastomosis facilitates low anterior resection for rectal cancer^{5,6,8,9,21,22}. This study suggests that the double stapling technique can be performed with a very low risk of isolated pelvic recurrence. The incidence of local recurrence of rectal cancer depends primarily on meticulous technique and adequate clearance of the tumour, and is probably independent of the method of colorectal anastomosis^{11,12}.

Acknowledgements

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Timing and method of reversal of Hartmann's procedure

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The outcome of 145 patients undergoing Hartmann's resection between 1973 and 1989 has been reviewed. The mortality rate of the primary procedure was 8 per cent. Eighty patients proceeded to reanastomosis. Multifactorial analysis of these patients was undertaken to determine the risk involved. The interval between the primary and secondary procedures was found to be the most important factor. Six of 12 patients had clinical evidence of a leak when this interval was <3 months, compared with seven of 28 for 3-6 months, and none of 40 when the second operation was delayed for >6 months. All deaths (three patients) and clinical septicaemia (four) occurred in the two 'early' groups. All colovaginal fistulae (three patients) and strictures (three) were associated with stapled anastomoses. No association was found between the complication rate following reanastomosis and the initial pathology or grade of surgeon undertaking the secondary operation.

Hartmann's operation was originally described in 1923 as a procedure for resection of carcinoma of the lower sigmoid colon and upper rectum. It is now widely used in the treatment of acute complications of diverticular disease. Hartmann¹ proposed that a later second operation might be performed to anastomose the descending colon to the rectal stump, but this failed to achieve popularity because the procedure was often a formidable undertaking.

Delayed anastomosis is now a well established procedure, with approximately 55 per cent of patients undergoing this operation²⁻⁵. The second procedure is associated with a mortality rate ranging from 0 to 14 per cent; rates for anastomotic and other complications vary²⁻¹² from 0 to 75 per cent.

A retrospective analysis was undertaken to determine the factors associated with mortality and morbidity after reanastomosis.

Patients and methods

The notes of all patients who had undergone Hartmann's procedure in Southampton between 1973 and 1989 were reviewed to determine mortality and major morbidity following delayed anastomosis.

In patients who underwent reversal of colostomy, the following eight variables were recorded for analysis: age; sex; benign or malignant disease at primary operation; operative findings of purulent or faecal peritonitis or more localized disease at presentation; concurrent morbidity; duration of hospital stay for the initial Hartmann's operation; method of anastomosis (hand-sewn or stapled); and the interval between initial Hartmann's procedure and reversal.

Statistical analysis was performed using two different endpoints: the development of major anastomotic complications and the duration of postoperative hospitalization.

Major anastomotic complications were clinical evidence of a fistula or leak (i.e. excluding leaks demonstrable only on barium enema), anastomotic stricture requiring operation or dilatation, and post-operative anastomotic haemorrhage requiring blood transfusion.

Multivariate analysis was used to enable each factor to be assessed allowing for the statistical impact of the other seven.

Cox's proportional hazards method was used to analyse the relationship between the eight covariates and postoperative hospitalization. The probability of developing a major anastomotic complication was analysed by stepwise logistic regression. A model best fitting the observed data was generated using the statistical packages BMDPLR and BMDP2L (BMDP Statistical Software, Los Angeles, California, USA) and the eight variables were then examined.

Results

A total of 145 patients underwent Hartmann's procedure during the study period. The mortality rate was 8.3 per cent. Eighty of these patients subsequently underwent reversal after a median interval of 6 months. There were 44 women and 36 men, with a median age of 65 (range 42-91) years. Fifty-seven patients presented with diverticular disease, 19 with carcinoma and four with miscellaneous conditions.

After reversal, 18 patients developed major anastomotic complications (13 fistulae or leaks, three strictures and two haemorrhages). Of these, ten required subsequent permanent colostomy formation, four developed septicaemia and three ultimately died (Table 1). The median postoperative hospital stay was 13 (range 7-90) days. There were 78 other complications which were minor, or not directly attributable to the anastomosis. Only 28 patients had a completely uneventful recovery.

All three deaths occurred in patients who underwent reversal before 6 months, and all were >80 years of age with other serious morbidity. One patient had a myeloproliferative disorder and was diabetic; the other two had severe cardiovascular disease. In each of these patients the initial complication was dehiscence of a hand-sewn anastomosis. Overt septicaemia occurred in two and all three developed multiorgan failure with death occurring between 9 and 20 days after operation.

Multivariate analysis revealed that a prolonged interval (>6

Table 1 Complications and deaths in 80 patients undergoing early or late reversal of Hartmann's procedure

	Early group (n = 40)	Late group (n = 40)
Major anastomotic complications	15	3
Fistula or leak		
Colocutaneous	8	0
Colovaginal	3	0
Intrapelvic	2	0
Haemorrhage	1	1
Stricture	1	2
Permanent colostomy	9	1
Septicaemia	4	0
Deaths	3	0

Table 2 Complications in 40 patients undergoing early reversal of Hartmann's procedure

	Reversal at <3 months (n = 12)	Reversal at 3-6 months (n = 28)
Fistula or leak		
Colocutaneous	4	4
Colovaginal	1	2
Intrapelvic	1	1
Haemorrhage	0	1
Stricture	0	1

Table 3 Major complications for stapled and hand-sewn anastomoses

	Stapled (n = 29)	Hand-sewn (n = 51)
Fistula or leak		
Colocutaneous	1	7
Colovaginal	3	0
Intrapelvic	1	1
Haemorrhage	1	1
Stricture	3	0

months) before Hartmann's reversal was the only factor associated with a low incidence of anastomotic complications ($P < 0.0005$, $r = -2.93$, s.e. 0.99, $\chi^2 = 14.98$, 0 d.f.) and a short period of postoperative hospitalization ($P < 0.05$, $r = 0.52$, s.e. 0.26, $\chi^2 = 4.05$, 1 d.f.).

Protracted hospitalization (>28 days) after the initial operation was significantly associated with an increased incidence of major anastomotic complications ($P < 0.01$) at the subsequent procedure.

Forty patients underwent reversal later than 6 months ('late' group) with only three major anastomotic complications (two strictures and one haemorrhage); in particular, there were no leaks and no deaths (Table 1). The median postoperative hospital stay was 12 (range 7-27, mean 12.7) days.

Of the 40 patients who underwent reversal before 6 months ('early' group), 15 developed major anastomotic complications and three died (Table 1). The median postoperative hospital stay was 14 (range 9-90, mean 19.5) days.

In patients in the early group, 12 underwent reoperation before 3 months (Table 2). Six developed major complications (all fistulae or leaks) and their median hospital stay was 25 (range 11-90, mean 32.5) days. In the remaining 28 patients, undergoing reversal between 3 and 6 months, nine developed major complications (seven fistulae or leaks, one stricture, one haemorrhage).

The overall complication rates for hand-sewn ($n = 51$) and stapled ($n = 29$) anastomoses were not significantly different, with nine major complications in each group. Two distinctly different patterns of complications were revealed: all the colovaginal fistulae and strictures resulted from stapled anastomoses, whereas nearly all the overt colocutaneous fistulae and septicaemias, and all the deaths, occurred in the hand-sewn group (Table 3).

Colonic pathology and the severity of peritonitis (localized versus generalized) at the first operation did not significantly influence the development of major anastomotic complications.

Discussion

The overall mortality rate from Hartmann's procedure and its reversal in this study was 10.3 per cent. This compares well with results from other recently reported series²⁻¹².

Delaying the anastomosis may be beneficial for two reasons. A patient may become 'fitter' by waiting for at least 6 months after major surgery. This has been confirmed in studies of

muscle function and fatigue. The effects of prolonged hospitalization on nutritional status have been documented^{13,14} and the implications of poor nutrition for anastomotic healing are well recognized¹⁵. Many of these patients were in hospital for >3 weeks after initial surgery and a delay in recovery after a second operation can be expected.

Resolution of intra-abdominal sepsis and inflammation present at the initial presentation takes time. Collagenase activity in the vicinity of colonic anastomoses is recognized¹⁶ and an increase in this is associated with the presence of infection¹⁷⁻¹⁹. The balance between formation and breakdown of collagen in the immediate postoperative period influences anastomotic healing²⁰. This is consistent with the influence of the timing of anastomosis, since intra-abdominal infection often persists long after the diseased colon has been removed. Obvious residual abscesses were found in six patients at the second operation. All of these were in the early group; two patients subsequently developed fistulae.

Patients with generalized peritonitis at the time of initial operation might be expected to fare worse following reversal than those with localized disease. This was, however, not found to be the case, suggesting that presence of sepsis at the site of the anastomosis alone is sufficient to impair healing.

Geoghegan and Rosenberg²¹ have reported that early anastomosis does not increase the risk to the patient, although those offered early restoration were a selected group of patients who had no evidence of intra-abdominal sepsis, nutritional depletion or active medical conditions that could improve with time. The same complication rate was reported in each group: 39 per cent for delayed and 35 per cent for early anastomosis. This is comparable to the 38 per cent complication rate for early restoration, but not that of 8 per cent for anastomosis delayed for >6 months, in Southampton patients.

The striking difference in the complication rates between the early and late groups accounted for the gross differences in the duration of hospitalization after operation.

A different pattern of complications occurred for hand-sewn and stapled anastomoses. All three strictures followed stapled anastomosis and this is a well documented complication²²⁻²⁴. All colovaginal fistulae also occurred following stapled anastomosis. Stapling in the septic pelvis may predispose to catching the posterior wall of the vagina in the staple line, leading to fistulation. Colocutaneous fistulae occurred more commonly with hand-sewn anastomoses, presumably because more of these were performed above the level of the pelvic peritonea, reflection.

These findings are of importance for the well-being of patients undergoing Hartmann's resection and reversal. They may prevent avoidable complications which increase the cost of the original procedure²⁵.

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Errata

Editorial errors unfortunately led to incorrect listings of the authors for three abstracts in the Eurosurgery '92 Supplement. Corrected versions are shown below.

Wouters DB. Arthroscopic fixation of osteochondral fragments with biodegradable material. *Br J Surg* 1992; **79**: S106.

Tocchi A, Basso L, Costa G, Lepre L, Liotta G, Mazzoni G. Canine model to study exocrine pancreatic pathophysiology. *Br J Surg* 1992; **79**: S112.

Tocchi A, Basso L, Costa G, Lepre L, Liotta G, Mazzoni G. Improved surgical decision making for pancreatic pseudocysts. *Br J Surg* 1992; **79**: S114.

The Journal apologises for any confusion caused.

Comparison of minimal and conventional surgery in patients with bleeding peptic ulcer: a multicentre trial

Sir

We read with great interest the paper by Poxon *et al.*, which compared minimal with conventional surgery in patients with bleeding peptic ulcers (*Br J Surg* 1991; **78**: 1344–5). This prospective randomized multicentre trial, conducted by 19 surgeons from three countries, concluded with the statement that 'in view of the high rates of fatal rebleeding after conservative surgery in this interim analysis, a decision to stop entry into the trial has been made'. Looking carefully through this paper we have some problems in accepting this harsh conclusion.

Rebleeding occurred following minimal surgery in seven patients, six of whom died. Four patients, all treated conventionally by oversew with vagotomy and pyloroplasty, experienced non-fatal episodes of rebleeding. Nowhere is it mentioned which ulcers rebled: gastric or duodenal? Gastric and duodenal ulcers are not similar in their suitability for under-running of the craters. Careful under-running of a large duodenal ulcer can be awkward and great care must be taken not to include the nearby common bile duct. Under-running of a gastric ulcer, on the other hand, is simpler: no vital structures lie in its vicinity and the crater can often be easily obliterated (or excised). If most of the fatal rebleeding in the study originated from duodenal ulcers then the authors' conclusion is not valid concerning minimal surgery for gastric ulcers.

All four patients in the conventionally treated group who experienced ulcer rebleeding following vagotomy and pyloroplasty and under-running (presumably of duodenal ulcers) survived. No data are given as to the severity of acute illness in these cases. Perhaps their better general condition allowed them to survive the recurrent haemorrhage. Alternatively, it is possible that different facilities in the 12 participating hospitals (e.g. patient monitoring for further haemorrhage, intensive care facilities and others) resulted in fatalities in some rebleeders and survival in others.

Mortality rates in the two groups were not significantly different. It appears that the authors 'traded off' deaths from rebleeding in the minimal surgery group for deaths from cardiovascular and septic causes in the conventionally treated group (related to the greater magnitude of the procedure?).

We have previously reported 27 patients with bleeding gastric ulcers treated with under-running alone. Only one of them rebled (4 per cent), and two died (7 per cent) from medical causes^{1,2}. Our experience with under-running for gastric ulcer now extends to a further 16 cases. Of these, one patient rebled and another died from medical causes.

The authors should be congratulated for their attempt to resolve this controversy. However, their apparently randomized trial, which fails to score objectively the severity of the illness of the patients and ignores important differences between gastric and duodenal ulcers, does not add significantly to our knowledge. We remain unconvinced that simple under-running is not an excellent solution for the high-risk patient bleeding from a gastric ulcer.

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Authors' reply

Sir

The null hypothesis for this study was that there is no difference in rebleeding and death between minimal or conventional surgery for bleeding peptic ulcer.

Results clearly showed that the only significant difference between the groups was fatal rebleeding. In the minimal surgery group, four patients with gastric ulcers rebled (all died) and three with duodenal ulcers rebled (two died). For conventional surgery, three patients with gastric and one with duodenal ulcers rebled.

The decision to stop entry into the trial was based on this difference in mortality (highlighted by monitoring deaths), while accepting that the high mortality rate following minimal surgery may have been caused by differences in standards of care or experience in treating these seriously ill patients. Indeed, such differences may be more important than the type of surgery performed and are a drawback of multicentre trials.

We acknowledge the excellent figures from Glasgow and wish to point out that in our own unit where there is an integrated policy of medical and surgical management, 37 patients (19 with gastric ulcers, 18 with duodenal) were entered into the trial. Of these, nine with gastric and seven with duodenal ulcers received minimal surgery. Three patients died: one from a gastric ulcer rebleed (minimal surgery group) and two from cardiovascular problems (one with gastric ulcer in the minimal surgery group, one with duodenal ulcer in the conventional group). Our overall mortality rate was 8 per cent and compares with an overall rate of 29 per cent where no defined policy existed in all other centres.

We therefore stand by our decision to end the study and regard simple under-running as a safe option provided that predictive risk factors for rebleeding (e.g. ulcer size, a visible vessel) are taken into account, that surgery is adequately performed and that facilities are sufficient to monitor these patients before and after operation.

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The Golden Glove Award

Sir

Despite the subsequently revolutionized surgical practice, I think Dr Halsted had even more at stake on a personal basis than outlined in your Announcement (*Br J Surg* 1991; **78**: 1241). I quote¹:

'In the winter of 1889 and 1890 – I cannot recall the month – the nurse in charge of my operating room complained that the solutions of mercuric chloride produced a dermatitis of her arms and hands. As she was an unusually efficient woman, I gave the matter my consideration, and one day in New York requested the Goodyear Rubber Company to make as an experiment two pairs of rubber gloves with gauntlets.'

He married the sad nurse, Miss Caroline Hampton, very shortly afterwards on 4 June 1890.

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Prospective audit of an extramucosal technique for intestinal anastomosis

Sir

I was interested to read the paper by Carty *et al.* on single-layer (extramucosal) anastomosis (*Br J Surg* 1991; **78**: 1439–41). Halsted's paper¹, which was published in 1887 and not 1987 (pp. 436–61 and not 817–22), reported experiments in dogs in which he arrived at a single-layer method of anastomosis using presection (before division of the bowel) quilt (horizontal mattress) stitches, avoiding the mucosa but with some inversion. The main thrust of Halsted's paper was to emphasize the hitherto overlooked importance of the submucosa ('an exceedingly tough, fibrous membrane') in terms of suture placement:

'... my experiments have led me to attach great weight ... to an accurate knowledge of the thickness and physical characteristics of the submucous coat of the intestine'.

Writing 35 years later, Halsted² was unprepared to affirm that for colonic anastomosis in humans, one layer of mattress sutures was better than two and had come to favour considerable inversion of the bowel ends – 'the deeper the turn the better'.

We did not 'reappraise' Halsted's technique but devised a technique that evolved over the years into what is correctly described as 'single-layer appositional serosubmucosal anastomosis'. The term serosubmucosal is more accurate than, and preferable to, 'extramucosal' since it reiterates the importance of the submucosa.

Sixty years ago in the UK, Wilkie³ was anastomosing the large bowel with a single layer of inverting linen Lembert stitches using an 'aseptic' method over clamps similar to those later described by Wangenstein⁴. The Wangenstein closed technique, introduced to Aberdeen in 1958 by H. A. F. Dudley, was used here for many years for small bowel and ileocolic anastomosis. In 1968 we began to use single-layer anastomosis in the large bowel. The closed technique was used whenever the bowel ends were sufficiently accessible but colorectal anastomoses were made open, at first with inverting sutures but since 1975 with appositional ones. A few years later the closed technique was discarded in the large bowel although we continued to use it for small bowel and ileocolic anastomosis for some more years. Despite its aesthetic appeal we have not used closed anastomosis since 1984, being convinced that open appositional serosubmucosal anastomosis is theoretically and practically more sound for all intestinal anastomoses. This technique, which evolved over several years in Aberdeen, appears to have been adopted in Basingstoke although not in detail. We have not used silk for more than 20 years in favour of braided polyamide, originally mounted on a series of threaded needles, but for several years now in the form of 3/0 (no. 2 metric) control release sutures (C-513; Ethicon, Edinburgh, UK), which are ideal for serial insertion before knotting. The precise details of the technique as applied to colorectal and ileocolic anastomosis are illustrated in two colour atlases^{5,6}.

We use the serosubmucosal appositional technique for all colorectal anastomoses and avoid a protective colostomy. Although Carty *et al.* prefer stapling for low colorectal anastomoses, the quoted reference⁷ gives a clinical leak rate of 18 per cent and a covering colostomy was regarded as essential.

The title of our 1976 publication⁸ is incorrectly quoted. It should read 'Single layer anastomosis in the gastrointestinal tract' and refers to 205 elective anastomoses not 204 elective cases. In a more recent publication⁹ 466 elective and emergency anastomoses in the upper gastrointestinal tract were complicated by leakage in 1.3 per cent. We have not written specifically on the results of emergency large bowel anastomosis, in which judgement for or against making an anastomosis is an important factor in outcome. However, in a report¹⁰ of the results of immediate resection in emergency large bowel surgery between 1977 and 1983 an immediate anastomosis was made in 46 of 82 patients (56 per cent) with a leak rate of 2.2 per cent.

Despite our advocacy of interrupted serosubmucosal sutures, the large bowel (excluding low colorectal anastomosis) may also be anastomosed with excellent results using a single-layer continuous polypropylene suture that includes a minute bite of mucosa¹¹. The common features between this and our technique are a single layer of suture material and apposition of the bowel ends. The latter may be more important than the former. As Halsted² said: 'The last word on the subject of intestinal suture may some day be written.'

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Preoperative chemotherapy for cancer of the oesophagus

Sir

The outlook for patients with oesophageal cancer undergoing surgery with curative intent remains poor. Failure of therapy is the result of both local recurrence and distant metastases. Chemotherapy given before surgery thus has the potential to improve the results of the operation and reduce subclinical metastatic disease.

There is increasing evidence from phase II studies that oesophageal cancer can respond well to cisplatin-based combination chemotherapy. Response rates to chemotherapy before surgery appear to be in the range of 40 to 60 per cent for squamous carcinomas and 30 to 40 per cent for adenocarcinomas^{1–3}. No randomized trials have yet been completed to establish whether neoadjuvant chemotherapy prolongs survival, but the International Organisation for Statistical Studies of Diseases of the Oesophagus and the North American Intergroup are currently conducting trials involving chemotherapy in patients with resectable squamous carcinoma in which chemotherapy is given both before and after operation.

The British Medical Research Council Oesophageal Cancer Working Party has recently opened a multicentre prospective randomized trial comparing surgery with or without preoperative chemotherapy consisting of two courses of cisplatin 80 mg/m² on day 1 plus fluorouracil 1 g/m² on days 1 to 4 (total dose 4 g/m²), with an interval of 3 weeks between the courses. Cisplatin and fluorouracil are two of the most active single agents in both squamous carcinoma and adenocarcinoma and are known to be effective in combination. It is intended to randomize 800 patients with resectable squamous carcinoma, adenocarcinoma, or undifferentiated carcinoma involving the upper, middle, or lower thirds of the oesophagus or cardia, but not postericoid tumours.

The main endpoint of the trial is survival, and the design is simple to encourage widescale collaboration. We are eager to enlist as many centres as possible throughout Europe and internationally. Potential participants can obtain details and copies of the protocol (OE02) from Dr Girling at the MRC Cancer Trials Office.

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Importance of unilateral absence of the vas

Sir

The letter from Messrs Heaton and Nawrocki concerning the unilateral absence of the vas (*Br J Surg* 1991; **78**: 1510) is interesting. They state that this condition is present in 0.5 to 1 per cent of the population. It may be of interest that I have performed over 8000 bilateral vasectomies, and have found a unilateral absent vas on only two occasions, both of which were in patients with undescended testes. If the figures of Heaton and Nawrocki are correct, I should have found between 40 and 80 patients with unilateral absence of the vas.

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Management of the perineal wound following abdominoperineal resection: prospective study of three methods

Letter 1

Sir

We read with interest the article by Robles *et al.* on the management of the perineal wound following abdominoperineal excision (*Br J Surg* 1992; **79**: 29–31). We appreciated the healing rate of 85 per cent after primary closure of the perineum combined with abdominal drainage. However, we are astonished that so many relatively young patients with Dukes' A and B rectal tumours underwent abdominoperineal excision of the rectum. The results in many reports have not shown any benefit for abdominoperineal excision over low anterior resection or a coloanal anastomosis with regard to local recurrence or survival rate^{1,2}. As a consequence, we have almost completely abandoned the perineal dissection even in patients who for reasons of extreme age, weak sphincters or general illness are less suitable for an anastomosis. After dissection of the pelvis according to Heald and Ryall³, we continue in the intersphincteric plane and close the remnant of the anal canal (at the level of or below the dentate line) from above, using a stapler. We then place an abdominal sump drain in the presacral cavity with continuous suction (15 cmH₂O) for 24–48 h.

Using either low anterior resection, coloanal anastomosis or abdominal excision there are only a few patients with low and large Dukes' C rectal tumours or rectal Crohn's disease who are left for perineal excision.

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1. Williams NS. The rationale for preservation of the anal sphincter in patients with low rectal cancer. *Br J Surg* 1984; **71**: 575–81.
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Authors' reply

Sir

The comments by Drs Liljeqvist and Gullberg are not related to the aim of our paper, which referred exclusively to patients undergoing abdominoperineal excision. In the same period (January 1985 to December 1989) another 89 patients with adenocarcinoma of the rectum underwent anterior resection, a proportion that has risen over the past few years, although only for rectal tumours in the middle or upper third (> 5 cm from the anal margins). For tumours in the distal third (< 5 cm from the anal margins), we generally favour abdominoperineal excision, with careful selective indications for sphincter-conserving techniques.

Of the 102 patients in our original article, 76 had a tumour in the distal third and 26 in the middle third; of the latter, 24 were Dukes' class C.

Lastly, and in relation to the aim of our paper, we note that they favour drainage of the presacral cavity, with suction drains brought out through the abdomen and maintained for 24–48 h.

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Letter 2

Sir

I read with interest the article by Robles *et al.* (*Br J Surg* 1992; **79**: 29–31). I take issue with the siting of the perineal drains in group 2. Drainage tubes brought out through the ischiorectal fossae cause unnecessary postoperative discomfort because patients cannot avoid sitting on them. This discomfort lasts long after the drains have been removed and is particularly severe if infection develops at the site of the drain. These drains can easily be brought out more anteriorly away from pressure points.

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Letter 3

Sir

We were interested to read the report of Robles *et al.* (*Br J Surg* 1992; **79**: 29–31) on the closure of the perineal wound after abdominoperineal resection of the rectum.

In our unit we use primary closure of the pelvic peritoneum and perineum, with a corrugated drain brought through the latter unless bleeding or contamination indicate packing. We were surprised to see that a similar approach in the authors' hands resulted in a mean hospital stay of 23.7 (range 13–40) days. We have therefore reviewed our experience over the past 4 years (1988–1992) of the same type of patients as those studied by the authors. In our hands this policy resulted in a mean hospital stay of 13.0 (range 7–27) days in 32 patients. These data compare very favourably with method 3 of Robles *et al.* (primary closure of the perineum with transabdominal drainage of the presacral space). We wonder whether bias was introduced into the allocation of patients to each management group by the lack of randomization, and feel that the recommendation of transabdominal drainage as the method of choice must be made more reservedly.

As regards the statistical methods, we wonder whether non-parametric analysis should have been used for the differences in hospital stay. The high standard deviations in these data and the small numbers of subjects indicate that this would be more appropriate.

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Authors' reply

Sir

We agree with Mr Widdison's comment that perineal drains can be brought out more anteriorly with a consequent reduction in postoperative discomfort of group 2 patients (undergoing primary closure of the perineum and perineal drainage).

With respect to the comments of Lewis *et al.*, our results show a longer postoperative hospital stay for group 2 patients than in their series. We do not know their rate of infection but our patients had a high rate of perineal wound infection (47 per cent) with method 2, which made partial or complete opening of the perineal wound necessary. This led to a longer hospital stay.

Our patients were not randomized, although the study was done prospectively, requiring that the three series be homogeneous with respect to age, sex and histological degree of malignancy. A non-parametric test could be used for the differences in hospital stay but the statistical test used is robust and the conclusions identical with either method.

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Easy delivery of the gallbladder in laparoscopic cholecystectomy: a grooved director

Sir

We note the use made by Williams *et al.* of a grooved director and scalpel to aid delivery of the gallbladder without enlarging the abdominal wound during laparoscopic cholecystectomy (*Br J Surg* 1992; 79: 344).

It has been our practice to use a pair of heavy curved scissors which are available on the laparoscopic cholecystectomy tray to assist with this manoeuvre. After delivering the neck of the gallbladder into the wound, this instrument is passed over the fundus under direct vision into the peritoneal cavity (the curve makes this easier). Opening the scissors under vision allows controlled stretching of the peritoneum and facilitates delivery of the gallbladder with minimal risk of perforation. This technique requires no additional instruments, allows delivery of large stone loads without enlarging the skin incision, and undoubtedly saves time at the end of the procedure.

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Adjuvant herbal treatment for gallstones

Sir

Savage and colleagues' thesis (*Br J Surg* 1992; 79: 168) that 'olive oil and lemon juice may be considered as an adjuvant to gallstone lithotripsy or to shorten the course of treatment with oral dissolution agents' must surely have been written with tongue in cheek. It is as scientific as their assertion that the herbalist involved 'was not aware of any case of recurrent gallstones'. Spontaneous passage of small stones through the ampulla and migration of large stones via fistulae are well documented. However, the authors should have: (1) produced their ultrasonograms demonstrating the four 2.5-cm stones as well as multiple small ones; (2) analysed the stones retrieved by the patient on sieving his stools; and (3) performed early 'postevacuation' ultrasonography to demonstrate their disappearance. They do not have as they claim 'clear ultrasonographic evidence of a reduction in the number of gallstones following the ingestion of olive oil and lemon juice.'

We have experience of a 64-year-old man with cholelithiasis awaiting cholecystectomy. He took the 'olive oil and lemon cure' and returned with a jar containing multiple 'stones'. Examination, however,

proved these stones to be faecaliths, presumably evacuated from his colonic diverticula during the massive purgation. Further examination proved that his gallstones were still in the gallbladder and he proceeded to uneventful cholecystectomy.

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Authors' reply

Sir

Mr Johnston is correct in his assumption that our Case Report was written 'with tongue in cheek'. We did not feel the need to burden the Journal with the necessity to print two ultrasonograms; in this the Editors tacitly agreed. The sonograms did show multiple small and large gallstones on the initial scan and a solitary large stone on the subsequent scan, a finding that was confirmed at operation. Therefore there was clear ultrasonographic evidence of a reduction in the number of gallstones. We were not in a position to perform 'early post-evacuation' ultrasonography. Nor were we in a position to analyse the stones retrieved. Had we been able to make such analyses, we would of course have subjected our patient's stones to the same rigorous chemical and scientific analysis as performed by Mr Johnston for his patient's stones.

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Parietal seeding of carcinoma of the gallbladder after laparoscopic cholecystectomy

Letter 1

Sir

We read with interest the Case Report by Pezet *et al.* (*Br J Surg* 1992; 79: 230). This provided an excellent example of the potential risk of parietal tumour cell dissemination when using laparoscopic techniques to deal with intra-abdominal malignancy.

Contrary to the statement in the article the first report of parietal seeding on the periumbilical trocar site from carcinoma of the gallbladder following laparoscopic cholecystectomy was originally published¹ in December 1991. The patient developed a firm soft tissue mass at the umbilicus 15 weeks after laparoscopic cholecystectomy, excision biopsy of which showed metastatic carcinoma.

Laparoscopic cholecystectomy has quickly emerged as a popular alternative to the open operation for symptomatic cholelithiasis since its introduction in 1988. Recent developments in laparoscopic instrumentation and increased surgical experience have resulted in the elimination of many former exclusion criteria for laparoscopic cholecystectomy. However, we strongly believe that preoperative diagnosis of gallbladder carcinoma (4.3–19 per cent of patients with biliary pathology²) constitutes an absolute contraindication to this procedure.

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Letter 2

Sir

We read with interest the article on parietal seeding of carcinoma of the gallbladder after laparoscopic cholecystectomy by Pezet *et al.* (*Br J Surg* 1992; **79**: 230) and would like to share their concern by reporting a similar case. A 73-year-old woman with recurrent biliary colic had an ultrasonographic scan that revealed the presence of two stones in a thick-walled gallbladder and a dilated common bile duct (11 mm) containing no stones. There was no history of jaundice and results of liver function tests were normal. Laparoscopic cholecystectomy was performed in October 1991 using a standard four-port technique and diathermy dissection. The gallbladder was adherent to the gastric antrum and dissection was difficult though uneventful; the patient was discharged home the following day. Histological examination showed a moderately differentiated adenocarcinoma of the gallbladder infiltrating on to the serosal surface (stage IV). In view of the poor prognosis in this particular instance we decided simply to follow up with computed tomography at 4 months to reassess the local situation rather than proceed to aggressive surgery. However, the patient presented 3 months later with a large deposit in the epigastric port where the gallbladder had been delivered and another deposit in the right upper quadrant causing gastric outlet obstruction. She underwent gastroenterostomy and resection of the abdominal wall deposit. Histological examination showed a metastatic poorly differentiated adenocarcinoma. The patient became jaundiced, her condition deteriorated, and she died within 6 months of the first operation.

We suggest that routine use of a non-porous Espiner-type bag for retrieval of the gallbladder after laparoscopic cholecystectomy could reduce the incidence of wound seeding in these cases. Otherwise we agree with Pezet *et al.* that resection of the trocar site immediately after diagnosis may be helpful when the tumour is confined to the gallbladder wall and the prognosis is more favourable.

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Bile duct injury following laparoscopic cholecystectomy

Letter 1

Sir

We read with interest the Case Report by Cheslyn-Curtis *et al.* (*Br J Surg* 1992; **79**: 231-2) on bile duct injuries sustained during laparoscopic cholecystectomy. We have recently operated on three patients with bile duct injury occurring during laparoscopic cholecystectomy. We propose a third mechanism of injury to the bile ducts as well as transection and clip obstruction.

The first patient was a 40-year-old woman in whom transection of the common bile duct (CBD) occurred during laparoscopic cholecystectomy. This was recognized at surgery which was converted to an open procedure. End-to-end repair of the CBD was performed over a T tube. The patient initially made a good recovery and the T tube was removed 5 weeks later. After a further week, she developed obstructive jaundice. Percutaneous transhepatic cholangiography showed a stricture of the common hepatic duct (CHD) 1 cm below the junction of the hepatic ducts. At operation a hepatodochojunostomy Roux-en-Y was performed using the mucosal graft technique over a transhepatic tube, and following its removal 4 months later the patient has remained well.

The second patient was a 35-year-old man who underwent apparently uneventful laparoscopic cholecystectomy. He was readmitted a few days later with abdominal pain and jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) showed blockage of the CHD and at laparotomy a tangentially placed clip was noted across the CBD at the level of the cystic duct. The CHD could not be identified. A sutured hepatodochojunostomy Roux-en-Y was performed without a transanastomotic splint. The patient subsequently developed a biliary fistula via the drain placed near the anastomosis. He developed Gram-positive sepsis. Percutaneous transhepatic cholangiography showed contrast flowing from the CHD to a cavity around the bile ducts and out through the drain. At surgery, the CHD was identified, and a mucosal graft hepatodochojunostomy using the already established Roux-en-Y and a transhepatic tube was performed. Thereafter the patient made an excellent recovery.

The third patient was an 18-year-old woman who underwent apparently uneventful laparoscopic cholecystectomy. She developed jaundice 12 days after operation, associated with abdominal distension. ERCP was performed which showed a complete block of the CHD. Abdominal ultrasonography confirmed a bile collection in the upper abdomen which was drained percutaneously. At laparotomy, the CHD had necrosed, leaving only part of the junction intact. The hepatic ducts were only 1 mm in diameter, precluding the passage of a transhepatic tube. A sutured hepatodochojunostomy was constructed over a transanastomotic Silastic (Dow Corning, Reading, UK) tube passed into the left hepatic duct situated so that the side holes of the tube drained the right hepatic duct, and the tube brought out through the Roux-en-Y to the exterior. Thereafter the patient made an excellent recovery and remains well 6 months later.

Our experience of bile duct injury complements that of Cheslyn-Curtis *et al.* and illustrates a further mechanism of injury to the bile ducts. The first case demonstrates transection of the CBD, the second obstruction caused by metal clips and the third that overzealous diathermy stripping of bile ducts may lead to necrosis. We agree that bile duct injury is not always apparent at the time of laparoscopic cholecystectomy and that the results of this technique should be adequately audited. We feel that the learning curve is longer than initially thought and that too many surgeons fail to convert to open operation in the face of anatomical uncertainty or technical difficulty.

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Letter 2

Sir

In a recent article Cheslyn-Curtis and colleagues (*Br J Surg* 1992; **79**: 231-2) correctly refer to the risk of bile duct injury associated with laparoscopic cholecystectomy. In both the cases of bile duct injury reported, however, it would appear that operative cholangiography was not undertaken or attempted at the time of the initial surgery.

Bile duct injury associated with open cholecystectomy has been linked in the past with surgical inexperience¹ and the lack of operative cholangiography². There is no reason to suspect that the same risk will not apply to the laparoscopic procedure. The majority of surgeons in the UK undertaking laparoscopic cholecystectomy are still in the 'inexperienced' category as 75 per cent have performed fewer than 50 procedures and nearly half never undertake operative cholangiography (recent nationwide questionnaire to Association of Surgeons Fellows, unpublished). The risk of iatrogenic major bile duct damage in their hands is thus compounded. Most surgeons performing laparoscopic cholecystectomy may not attempt operative cholangiography as they have never been trained to do so or may consider it a technically difficult and time-consuming procedure. It is indeed possible for operative cholangiography to be successfully and easily undertaken laparoscopically in <5 min. Frequent utilization of the technique will familiarize the surgeon so that the procedure can be undertaken in both easy and difficult cases. The first time to perform a laparoscopic cholangiogram should not be in the emergency situation.

Eighteen months ago most surgeons embarking on laparoscopic cholecystectomy were novices, and the bile duct injuries associated with their learning curves bear testimony to this. Training will continue and more surgeons will embark on the procedure of laparoscopic cholecystectomy. It is unfair to subject patients repeatedly to a learning curve without attempting to minimize complications of what is an essentially simple and rapid technique.

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Book reviews

Color Doppler Flow Imaging

W. D. Foley. 285 × 220 mm. Pp. 175. Illustrated. 1991. Oxford: Butterworth-Heinemann. £95.

This is not a book for the reader with a casual interest in the subject of colour Doppler flow imaging (CDFI). The introductory chapter makes few allowances for any innate deficiency in a knowledge of the physics involved in ultrasonography or the Doppler effect. However, for practitioners with minimal experience in the field, the early pages do explain in a rational manner some of the difficulties of interpretation and the solution to such problems. There is relatively brief mention of spectral analysis and the derivation of pulsatility and resistive indices.

The subsequent chapters deal with the use of CDFI in various regions of the body, for example the neck, orbit and neonatal brain, abdomen, abdominal transplants, extremity arterial disease, extremity venous disease and the genitourinary system. Each chapter briefly describes the appropriate instrumentation and scanning techniques and then details in more depth the results obtained by examination of pathological states. The scanning images are explained on the basis of commonly seen disorders and illustrated by finely reproduced illustrations of scans obtained with CDFI. These illustrations are a significant strength of the book and make it a reference volume that will be invaluable for those users with limited experience of the technique.

I would have preferred to have read some applications of spectral analysis but the author prefers to concentrate on an evaluation of imaging. One of the attributes of the technique is that the imaging is relatively reproducible and since it is not invasive can be repeated and used to follow the course of disease or therapy. It is somewhat disappointing that the author does not review the application of CDFI to the clinical management of vascular disease; its whole value cannot be truly assessed. Perhaps it is too early to make this evaluation and authoritative reviews will only be possible when there are sufficiently experienced practitioners in the clinical disciplines capable of producing the quality of scan of which Dr Foley seems capable.

Although there is an acknowledged plateau of performance of the technique, it is not improbable that CDFI will give improved imaging in the future and replace a great deal of contrast vascular radiology. Used in combination with interventional radiological technology, a number of procedures formerly carried out in the operating room will eventually be practised in the departments of imaging.

The late Professor G. R. Giles

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A Short Textbook of Surgery. 1st ed.

Roshan Lall Gupta. Illustrated. 1991. India: Jaypee Brothers Medical. 175 rupees.

This short textbook is long on facts, common sense and readability. It is a monograph, with the exception of two chapters written by Mr Paul Atkins, aimed primarily at undergraduates in the Indian subcontinent. The style is lucid and simple, the layout appealing and uniform, and the artwork graphic and plentiful.

The book opens with nine chapters on basic principles covering such time-honoured subjects as shock, wound healing, surgical infection, and fluid and electrolyte balance. Herein there is more than sufficient knowledge for the undergraduate, including a concise chapter on blood transfusion that introduces such topics as autotransfusion and the human immunodeficiency virus. Forty-four more chapters follow, each of ten to 20 pages, which deal with surgical disease on an anatomical basis from head (the scalp, skull, spine and nervous system) to toe (diseases of arteries). Urology and orthopaedics are also included.

Sampling the chapters reveals a uniform style that adds clarity, for instance the tumour node metastasis system for staging cancer is used for solid tumours, each organ-specific chapter begins with basic anatomy and embryology and thus passes naturally to congenital abnormalities. Consumption of later chapters is made easier by this approach. I was hard pushed to find omissions: Crohn's disease preceded amoebiasis, portal hypertension was cheek-by-jowl with hydatid cysts of the liver; even laparoscopic cholecystectomy received a mention.

The price of this book is extraordinarily good value at 175 rupees.

The publishers could find themselves overwhelmed if an equivalent priced English edition became available.

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Abdominal Intraoperative Ultrasonography

M. Makuuchi (ed.). Pp. 214. Illustrated. 1987. Tokyo: Igaku-Shoin.

In surgery, a main method of treatment is removal of pathology and a sound knowledge of anatomy is a prerequisite for a safe and successful operation. This is especially true when operating on the liver, where intraoperative ultrasonography can now provide the surgeon with an important demonstration of both normal anatomy and pathology. The editor of this book is a pioneer of intrahepatic ultrasonography and a highly experienced hepatic surgeon.

The book is in five parts and the quality of printing is excellent. There are many high-quality photographs and diagrams which serve to make the volume not only an informative book but also an illustrative atlas. The first three parts (ten chapters) take the reader smoothly from basic ultrasonographic anatomy of the liver, through the application of ultrasonography in performing hepatectomy, to its use in the resection of pancreatic insulinoma. The last two parts (two chapters) discuss the application of the technique in vascular surgery and the future of operative ultrasonography. Each chapter is followed by many relevant references. However, there are a few printing errors in the explanatory notes to some diagrams and sometimes relevant text and diagram are not on opposing pages. I wish there were a chapter on the basic physics of ultrasonography and image orientation. These last remarks apart, this book can be highly recommended both to those surgeons who already use intraoperative ultrasonography and to those who wish to start using it.

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Limb Amputation from Aetiology to Rehabilitation

R. Ham and L. Cotton. 216 × 138 mm. Pp. 229. Illustrated. 1991. London: Chapman and Hall. £13.95.

This is a paperback book which addresses the whole area of amputation and is aimed at anyone who has an interest in, or is involved in, amputation surgery. Comprising about 200 pages, it is extremely readable and provides an excellent source of information, especially for those surgeons who might not be so familiar with periampputation management, particularly in relation to limb fitting.

The book is divided into 12 chapters of which the first two are given over to the history of amputation and to examining the epidemiology of amputations. The book then progresses logically through indications for amputation, preoperative management and assessment, amputation surgery and postoperative management. Given that the vast majority of amputations in the UK and Ireland are performed for end-stage vascular disease, I would like to have seen a slightly longer section on alternatives to amputation, perhaps including some reference to thrombolysis. In particular, it would have been interesting to have had a little further discussion on the merits of primary amputation *versus* distal reconstruction. However, such detail would be difficult in a book of this size, the rest of which is really extremely well written and well researched. I particularly enjoyed the sections on prosthesis fitting and the emphasis on early mobilization and fitting. The McColl report is given appropriate attention and its conclusions highlighted.

Major limb amputation still remains a common operation in any vascular unit. It is unfortunately still true that insufficient attention is given to the amputee. This book goes a long way towards addressing the problems associated with the patient before, during and after

Book reviews

operation. I found it extremely useful and would heartily recommend it to all clinicians in any way associated with amputation surgery.

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Orthopaedic Anatomy and Surgical Approaches

F. W. Reckling, J. B. Reckling and M. P. Mohn (eds). 285 × 221 mm. Pp. 525. Illustrated. 1990. St Louis: Mosby-Year Book.

This book is outstanding and may even become a classic. It is a multi-author text firmly edited by an experienced orthopaedic surgeon, nursing instructor and professor of anatomy that combines regional morphology with commonly used surgical approaches. The anatomical sections studiously avoid the morphological relationships that fuel undergraduate disillusion and reside briefly in their short-term memories, concentrating rather on the key structures with which the surgeon must be familiar.

The surgical approaches address a range of requirements from arthroscopy to disarticulation and further emphasize the practical relationships of nerves and vessels learned only by hands-on experience. There is an excellent chapter on biopsy. The illustrations are clear and usefully include both longitudinal and cross-sectional data.

The text would benefit from a section on nerve exploration, in particular of the brachial plexus. The commonest error made by junior surgeons is poor positioning and siting of incisions. Apart from the spine and foot, these are less clear than other material covered, and would be improved by further illustration. Radiographic anatomy is well covered for the hip and could usefully be extended to sections on the shoulder and knee, particularly as the surgical approaches for capsular and ligamentous reconstruction are addressed so well. Relevant biomechanics is covered succinctly for the spine, and other sections could only benefit from similar attention. Finally, there is no mention about the postoperative care which is essential to allow repair of the structures divided during the surgical approaches described.

This is a timely volume that imparts more information than A. K. Henry in modern rather than Miltonian English. It is ideal for trainees preparing for exit examinations and merits a place on the bookshelves of all junior orthopaedic surgeons.

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Raynaud's Syndrome

E. D. Cooke, J. M. Porter and A. N. Nicolaidis (eds). 247 × 175 mm. Pp. 247. Illustrated. 1991. London: Med-Orion. £49.

It is a pity that the authors use the obsolete title of *Raynaud's Syndrome* instead of the better *Raynaud's phenomenon*. A syndrome is a characteristic group of symptoms and a phenomenon is an event that may be observed, e.g. the episodic digital arterial constriction of Raynaud's phenomenon. The editor's blue pencil has, in fact, failed to erase the use of Raynaud's phenomenon in several places in the book. This is a multi-author text, 29 authors in all, varying from experienced physicians to technical staff. Thus, although some parts are of value to clinicians, others are rather technical and of interest mainly to research workers.

The first seven chapters review the pathophysiology of Raynaud's phenomenon. The section on endothelium-derived relaxing factor is of particular interest as this is a growing point in the study of this condition. There are chapters on the association of Raynaud's phenomenon with underlying disease, e.g. scleroderma, and its prevalence in hospital-based study but, unfortunately, no adequate information (perhaps because it does not exist) on the true prevalence of primary and secondary Raynaud's phenomenon in the community.

The next section reviews in depth all the various techniques used in the investigation of Raynaud's phenomenon and is of particular use for researchers in the field.

The final section reviews the management of the condition with drugs, particularly thymoxamine. I was disappointed to find no chapter on general advice and non-drug measures, e.g. hand warmers, adequate heating, use of electrically heated gloves and so on, which is all the treatment that the great majority of patients with Raynaud's phenomenon need, or will accept.

These are, however, minor criticisms of a useful and informative book that deserves a place on the shelf of all vascular physicians and surgeons, and of anyone else, e.g. rheumatologists or dermatologists, who have to deal with this difficult condition.

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Medical and Surgical Diseases of the Pancreas

J. E. Valenzuela, H. A. Reber and A. Ribet (eds). 260 × 180 mm. Pp. 184. Illustrated. 1991. New York: Igaku-Shoin.

This is a beautifully produced little book with good illustrations and clear text. There are several useful flow diagrams and algorithms to describe management and investigation. However, I have some doubts about the usefulness of this book to the audience intended by its authors, who state in their preface that they are hoping to provide the practising physician, as well as medical students, residents and practising gastroenterologists, with a simplified update of new developments in pancreatic problems. They have certainly provided a simplified account of pancreatic disease, indeed one which is probably too didactic and under-referenced to be useful to the postgraduate. This book would be a good introduction to pancreatic disease for a bright final year medical student, but it lacks sufficient detail or discussion for the practising physician. For example, Chapter 2 is entitled 'Classification and pathology of acute pancreatitis'; it contains three pages of text and one macroscopic and one microscopic illustration. The discussion of the pathogenesis of acute pancreatitis focuses entirely on the activation of trypsin, with no mention of other current theories. Similarly, in the investigation and grading of severity of pancreatitis, there is no discussion of the recent advances that a physician with an interest in pancreatic disease might reasonably expect. There is no mention of the value of neutrophil elastase, trypsinogen activation peptide, or APACHE II score. I was disappointed with this book and would not recommend it for purchase by hospital libraries or those studying for postgraduate examinations.

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Baillière's Clinical Gastroenterology: Gastrointestinal Emergencies. Part 1

R. C. N. Williamson and J. N. Thompson (eds). 231 × 155 mm. Pp. 197. Illustrated. 1991. London: Baillière Tindall. £27.50.

Books in the *Clinical Gastroenterology* series are published quarterly. In this collection of eight essays (Part 1 of two) four chapters deal with the management of acute gastrointestinal problems and four with diagnostic techniques.

The first chapter reviews the management of oesophageal variceal bleeding. The range of endoscopic and surgical manoeuvres used in different units testifies to the continuing therapeutic difficulty that this condition causes. Dr Paul Swain's chapter on the endoscopic treatment of peptic ulcer haemorrhage moves from a review of the many techniques for achieving haemostasis to a valuable account of practical personal tips for endoscopists deep in at the red end. Concise reviews are provided from St Mark's Hospital of the management of true and false large bowel obstruction and from Kentucky on the role of surgery in abdominal sepsis.

Chapters follow on the contribution of radiological imaging and computer assistance to diagnosis in the acute abdomen. The late Professor Richard Stewart describes his research on peritoneal aspiration cytology of inflammatory cells. This vignette is an adaptation of diagnostic paracentesis, though unlikely to be widely adopted in clinical practice. The book concludes with an enthusiastic advocacy of the laparoscope in the acute abdomen. While many surgeons will continue to be selective in deciding which patients to submit to general anaesthesia and invasive investigation to find the cause of abdominal pain, few will resist the increasing intrusion of this valuable instrument into their practice.

This book is not a reference work on intestinal emergencies. The advantage of topicality of a quarterly publication is offset by the lack of substantial news in some of the subjects reviewed. A minor criticism is of the unnumbered reference system which disrupts the flow and

enjoyment of the text. In one short section there were eight references to the same paper. A more refined bibliography would not detract.

This book will be of particular use to surgeons and medical gastroenterologists preparing for higher exams. I enjoyed the opportunity to refresh my knowledge of the topics presented, and commend this book to those who would do likewise.

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Patterns of Hospital Medical Staffing – Trauma and Orthopaedic Surgery

R. Dowie. 296 × 210 mm. Pp. 48. Illustrated. 1991. London: HMSO Books. £6.45.

This report gives a detailed breakdown of the differing workloads, balance of elective and emergency surgery, and medical staffing in ten contrasting units varying from London teaching hospitals to small regional elective orthopaedic units. Several clear recommendations emerge. The plight of the senior house officer 'trainee' should be recognized and consideration given to staffing trauma services mainly by doctors in the staff grade. Preadmission clinics should be considered particularly in those units where there are no preregistration house officers and especially as day-case surgery is developed. The organizational separation of trauma from orthopaedic services generally allows more regulated provision of elective orthopaedic services, but where they are integrated it is suggested that there may be advantages in the appointment of a departmental practice manager to coordinate the use of beds and operating theatres.

This report should be required reading for all those managers and clinicians involved in service planning to enhance the understanding of the constraints and problems with which consultants and their teams are trying to cope. The woefully inadequate staffing of units outside the main teaching hospital centres is highlighted and it remains a wonder that so much high-quality orthopaedic surgery is carried out by so few.

Patterns of Hospital Medical Staffing – General Surgery

R. Dowie. 296 × 210 mm. Pp. 45. Illustrated. 1991. London: HMSO Books. £6.45.

This report is based on research in ten departments of general surgery in five health districts. While certain recommendations have been made from this study of the variation of caseloads in relation to available manpower and operating facilities, more meaningful conclusions might have resulted if weighting indices had been used to take account of the complexity of operative procedures and the service value of different members of staff.

The plight of the numerous surgeons performing registrar graded duties who are unlikely to follow a consultant career has been recognized and a possible role for them as staff grade surgeons in mainly elective surgical units organizationally separate from the main acute units has been proposed.

Preadmission clinics are recommended as a mechanism for reducing some of the burden of clerking that currently falls to preregistration house officers so as to enable the 72-h week to be achieved more easily. An audit of those emergency admissions not submitted to surgery and studies of the role of observation wards for acute admissions are recommended.

This short report should be required reading for all those concerned with planning to reduce the working hours of junior doctors, addressing the career ambitions of doctors working in the specialty, and helping to reduce waiting lists. It is detailed, authoritative and up to date.

Patterns of Hospital Medical Staffing – Overview

R. Dowie. 296 × 210 mm. Pp. 42. Not illustrated. 1991. London: HMSO Books. £5.60.

Robin Dowie is to be congratulated on the succinct and clearly written reports on hospital medical staffing. Her study took almost 5 years and is based on semistructured interviews with over 300 consultants and structured interviews with over 550 junior doctors in five health districts. Her description of the responsibilities for consultants in the 1990s outside their clinical obligations is up to date and comprehensive, omitting only the duties of Royal College appointed tutors and advisors

and those committed to teaching and writing, editing and reviewing papers for journals.

This overview raises several points for consideration by employing authorities, the medical colleges and the Department of Health. For consultants it will be necessary both to consider the provision of medical assistance to those appointed as directors of clinical directorates or clinical tutors, and to arrange programmes that enable them to be present in clinical areas with emergency workloads such as admission wards, labour wards and acute theatres. Furthermore, periods of time must be arranged for retraining in new techniques.

For junior doctors, the 72-h week needs to be implemented in the hard-pressed specialties and proper counselling arrangements set in place. It is also suggested that proper consideration should be given to the careers of experienced hospital doctors who do not wish or are unable to pursue a consultant career by reviewing the Joint Planning Advisory Committee 10-year target for posts in the staff grade.

This study concludes that there is much research to be done in medical manpower planning and the cost evaluation of medical staff, fields in health services research which have been neglected in the past. Let us hope that this concise yet authoritative and comprehensive report will be studied in detail by the new standing advisory committee that has been set up by Mr William Waldegrave to advise on the future balance of medical manpower supply and demand in the UK. This overview and its associated nine detailed reports deserve no less.

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Surgical Gems in Dermatology. Vol. 2

P. Robins (ed.). 236 × 160 mm. Pp. 131. Illustrated. 1991. New York: Igaku-Shoin. £42.

This little book is a compendium of tips (a more appropriate word than 'Gems') written by (mainly) American dermatologists. It covers a much wider span of treatment than most British dermatologists would be prepared to undertake, such as wedge excision of the lip and skin grafts round the back of the ear. It deals with the sort of technical procedures that are so pleasant and rewarding to discuss between papers at a scientific meeting.

There is a nice account of Fegan's method of treating varicose veins, and I was very interested in the idea of subcutaneous suction of the sweat glands to treat axillary hyperhidrosis. It was good to read a re-emphasis of the importance of controlled pressure in the neat healing of wounds, but the author writing on the treatment of keloids produces no evidence to support his method of treatment of a notorious condition. The use of gentian violet and cross scratching to aid accurate apposition of wounds would surely not be acceptable now in the UK, and I wonder if the author who claims that lipomas can be removed very simply under local anaesthesia has removed a big one from the back of the neck. Also, there are better ways of examining the male urethra than with an auroscope.

This book can be looked through with enjoyment by those working in a variety of surgical specialties who are senior enough to check each idea against their own experience. What the average British dermatologist will make of it, I am not quite clear.

J. Webster

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Pelvic Pouch Procedures

P. E. Thomas and T. V. Taylor. 253 × 193 mm. Pp. 191. Illustrated. 1991. Oxford: Butterworth-Heinemann. £45.

The advent of pelvic pouch procedures in the past 10 years has resulted in the establishment of anal sphincter-preserving techniques in several diseases of the colon and rectum. This concise book provides a summary of the technical developments and current problems in pelvic ileal and colonic pouch surgery.

The text is arranged in a logical sequence of historical perspective, technical aspects of pouch construction, clinical outcome and pathophysiological sequelae after restorative proctocolectomy. The line diagrams are clearly presented and complement the text. The book is extensively referenced, although a number of these (more than 10 per cent) are to work published in abstract form alone.

Book reviews

There is little doubt, with the greater ease of pelvic pouch construction and the increasingly successful management of the often serious postoperative complications, that patients are electing to undergo this procedure more readily than 5 years ago. Therefore, I would strongly recommend this useful book to those surgeons outside specialist units who are starting sphincter-preserving procedures in patients requiring proctocolectomy. For those units already established in the clinical and research aspects of pelvic pouch surgery, this text is a competitively priced, worthwhile addition to their libraries. My only criticism is that the review copy arrived 2 weeks after I had purchased the book independently.

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The Open Packing – Laparostomy in Pancreatitis and Peritonitis

H.-W. Waclawiczek, O. Boeckl and G. Pauser (eds). 234 × 156 mm. Pp. 324. Illustrated. 1991. Heidelberg: Springer-Verlag.

The management of patients with infected necrotizing pancreatitis is one of the more challenging problems the abdominal surgeon will be called upon to tackle. A multidisciplinary team approach is essential; death of the patient can occur for many reasons. However, failure is certain unless the abdominal sepsis is eradicated, which is particularly difficult to achieve because of the extensive and ongoing nature of the infection in the retroperitoneum. Simple drainage is usually ineffective; this has led to different surgical techniques. Broadly speaking these are laparostomy (leaving a pack in the open abdominal cavity and carrying out repeated debridements) or a closed technique with large drains and continuous irrigation.

This book is the report of a symposium held in Salzburg in October 1989. The long list of contributors come largely from Austria or Germany with a few from France, Switzerland and the USA. The first section is a pot pourri of contributions dealing with different pathophysiological effects of severe sepsis on the lung and liver, methods of 'hygienic' control of the patient, bacteriology and feeding. Some chapters are particularly short; none is fully comprehensive. The second section is a series of reviews from different units on their results of treating patients with varying degrees of necrosis and with different indications for operation. Bradley (Atlanta) is clear in his discussion about the extent of necrosis and infection in his patients and has excellent results with laparostomy. Beger (Ulm) has equally good results in patients undergoing continuous lavage of the pancreatic bed following debridement. Parc (Paris), adopting a surgical technique that lies roughly between the two, has a higher mortality rate but clearly feels he is dealing with more serious cases than Beger. The final section of the book deals with the principles of managing other forms of severe peritonitis.

There remains a need for a more detailed classification of such patients so that comparisons can be made. There is no clear answer from this book on the precise indications for surgery in different units. Infected necrosis may be one clear indication, but should the patient with adult respiratory distress syndrome have debridement of peripancreatic necrosis? (One contributor says 'yes', another 'no'.) Finally, this book points to the need for the concentration of such seriously ill patients in specialist units, which is how such experience has been built up on the continent with undoubted benefit to the patients.

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Cancer in Organ Transplant Recipients

D. Schmähel and I. Penn (eds). 236 × 156 mm. Pp. 182. Illustrated. 1991. Heidelberg: Springer-Verlag. DM 120.

This book is essentially the report of a conference held in Heidelberg in May 1990. It is difficult for a book derived from conference proceedings to give a balanced and complete picture of any topic, since

the end result depends on exactly who is able to attend the conference or submit abstracts, and the effort put into the subsequent paper by each author. Unfortunately, *Cancer in Organ Transplant Recipients* is a prime example of these drawbacks. The book contains some excellent contributions from acknowledged leaders in the field such as Penn, Schmähel and Hanto who give good overviews of the published literature in their areas. However, over half of the contributors were local and here the contributions are more variable, some being poor.

The book is almost entirely concerned with the incidence and prevalence of cancer, the distribution of its different types and the aetiology and prevention of the disease, but there is a considerable degree of repetition, particularly with regard to the role of viruses in cancer development. The title implies a broad overview of cancer in organ transplant recipients, and the most disappointing aspect of the book was the almost complete lack of information on diagnosis, management and outcome of cancer in this difficult group of patients. There is no index. In summary, this book provides a report of a recent conference on the problem of cancer in organ transplant recipients, and gathers together many of the relevant references in the field, with several good monographs. However, it is not a comprehensive reference text, and is likely to become rapidly outdated.

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Adjuncts to Cancer Surgery

S. G. Economou, T. R. Witt, D. J. Deziel, T. J. Saclarides, E. D. Staren and S. D. Bines (eds). 285 × 225 mm. Pp. 703. Illustrated. 1991. Philadelphia: Lea and Febiger. £102.

Surgical extirpation has long been regarded as the mainstay of treatment for solid tumours. However, improvements in surgical techniques have made only marginal improvements in overall survival rates. This book is based on the prevailing belief and oft-quoted hypothesis that increasing emphasis should now be placed on so-called 'adjunctive' aspects of treatment.

The editors have brought together 149 American and one European author to describe and discuss the various adjuncts under three headings: diagnostic, therapeutic, and support systems. The over-riding impression one is left with, however, is that the topics covered are broad but not particularly deep. For example, readers might be surprised that in a book of some 700 pages, only 20 are devoted to adjuvant radiotherapy and 35 to adjuvant chemotherapy.

All the major diagnostic methods are covered under appropriate headings, e.g. pathology (immunocytochemistry and flow cytometry), imaging, needle aspiration, endoscopy, laparoscopy and monoclonal antibodies. I found the chapter on new concepts and techniques in pathology to be a particularly valuable overview. It is written specifically from the point of view of how new techniques can help a surgeon decide, not only on diagnosis, but also on the most appropriate treatments. An example of such a dilemma is: 'The metastasis is a carcinoma, but where is the primary tumour?' A topic dealt with particularly well in the support systems section is the management of pain – a subject that surgeons are now taking far more seriously than in the past. The surgical aspects are covered under separate titles. Some readers may be intrigued to note that under 'Curative surgical adjuncts' are 'Liver transplantation for cancer' and 'Liver resection for metastatic cancer'. Surgery for oesophageal and gastric cancer are dealt with under 'Palliative surgical adjuncts'.

This book is not designed as a surgical textbook in the classical sense and therefore one should not expect detailed descriptions of surgical procedures. It could best be described as a comprehensive array of topics. It is an attempt to provide an encyclopaedic approach rather than focusing on specific topics, and therefore provides a broad picture of available adjuncts that surgeons might find useful when dealing with patients with cancer.

I. Taylor

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Notices and announcements

12 September 1992

Society of Minimally Invasive General Surgeons Autumn Meeting
Cambridge, UK

Information: Mr D. C. Dunn, Level 7, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

20–23 September 1992

VIIth Edmondo Malan International Day of Surgery – Endo-laparoscopic and Mini-invasive Surgery
Parma, Italy

Information: Professor Gian Carlo Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43100 Parma, Italy

20–24 September 1992

Combined Meeting of the Association of Surgeons of Great Britain and Ireland and Trinity College Dublin Quatercentenary Meeting
Dublin, Ireland

Information: Mr T. N. Walsh, Department of Surgery, St James's Hospital, Dublin, Ireland

22–24 September 1992

Fifth Meeting of the International Association of Pancreatologists and Fourth Meeting of the International Pancreatic Cancer Study Group
Athens, Greece

Information: Congress Secretariat, Dr C. Arvanitakis, First Medical Department, University of Thessaloniki, AHEPA General Hospital, 54 006 Thessaloniki, Greece

24–26 September 1992

Postgraduate Course – Principles of Colon and Rectal Surgery
Minnesota, Minneapolis, USA

Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue Southeast, Minneapolis, Minnesota 55414, USA

7–8 October 1992

VIIth National Conference of the Association of Paediatric Surgeons of Pakistan
Lahore, Pakistan

Information: Dr Z. B. Attar, Department of Paediatric Surgery, National Institute of Child Health, Karachi, Pakistan

8–9 October 1992

Second GI Tract Laparoscopic Surgery International Meeting
Liège, Belgium

Information: Catherine Marissiaux, Clinique St-Joseph, Chirurgie de l'Appareil Digestif, Rue de Hesbaye 75, B-4000 Liège, Belgium

15–16 October 1992

European School of Oncology 10th Anniversary Events
Milan, Italy

Information: European School of Oncology, Via Venezian 18, 20133 Milan, Italy

23 October 1992

Symposium – Extracranial Carotid Artery Surgery: Including Prevention of Stroke
London, UK

Information: Mrs Louise Brooks, Meadox UK Ltd, Matthew House, Matthew Street, Dunstable LU6 1SD, UK

27 October–4 November 1992

Anaesthesia and Surgical Intensive Care: Controversies and Conflicts
Bristol, UK

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

4–8 November 1992

American Association for Cancer Research – Genetics of Cancer
Hilton Head Island, South Carolina, USA
Information: American Association for Cancer Research, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, PA 19106-3483, USA

6–7 November 1992

International College of Surgeons 38th Annual Meeting of the Japan Section – 'Controversies in Surgery'
Tokyo, Japan
Information: Professor K. Kimura, Department of Surgery, Tokyo Medical College, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan

15–18 November 1992

Update and Future Trends in Fibrin Sealing in Surgical and Non-surgical Fields
Vienna, Austria

Information: Univ. Prof. G. Schlag, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstraße 13, A-1200 Vienna, Austria

15–21 November 1992

Advances in Cancer Treatment
London, UK

Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

16–20 November 1992

Research Methods in Surgery
London, UK

Information: Jacqui Searle, Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0NN, UK

16–21 November 1992

XXVIII World Congress of the International College of Surgeons
Cairo, Egypt

Information: EMECO Travel, 2 Talaat Harb Street, PO Box 1294, Cairo, Egypt

25–28 November 1992

Recent Advances in Anaesthesia, Pain, Intensive Care and Emergency
Trieste, Italy

Information: Trieste Traduzioni Congressi, Via C. Battisti 1, 34125 Trieste, Italy

3–5 December 1992

Special International Columbus Meeting on Surgical Oncology
Genoa, Italy

Information: Italiana Congressi, Via P. E. Bensa 2/6A, 16124 Genoa, Italy

4–5 December 1992

8th International Steglitz Paediatric Surgical Congress: Endoscopic Surgery in Children
Berlin, Germany

Information: Dr F. Schier, Kinderchirurgie, Universitätsklinikum Steglitz, Hindenburgdamm 30, 1000 Berlin 45, Germany

8–10 December 1992

Seventh International Workshop on Therapeutic Endoscopy
Hong Kong

Information: Dr S. Chung, Combined Endoscopy Unit, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong

10–11 December 1992

Reconstruction in Surgical Oncology
Genoa, Italy

Information: Anna Guida, Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV, 10–16132 Genoa, Italy

3–6 January 1993

Postgraduate Course in Gastroenterology
Oxford, UK

Information: Dr D. P. Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

7–8 January 1993

Surgical Research Society Meeting
London, UK

Information: Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

8–10 February 1993

Child Safety in Southern Africa
Cape Town, South Africa

Information: Deborah McTeer, Postgraduate Medical Centre, UCT Medical School, Observatory 7925, Cape, South Africa

18–20 February 1993

Colorectal Disease in 1993: an International Exchange of Medical and Surgical Concepts

Fort Lauderdale, Florida, USA

Information: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Room TT-31, Cleveland, Ohio 44195-5241, USA

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Phlebology Review
Lake Buena Vista, Florida, USA

Information: North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, CA 92024, USA

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